Universidade de Lisboa
Faculdade de Motricidade Humana

Effects Of Neural Tension In The Sciatic Nerve Stiffness, In Healthy People And People With Low Back Related Leg Pain

Tiago Gonçalves Neto

Orientador: Professor Doutor Raul Alexandre Nunes da Silva Oliveira
Co-orientador: Professor Doutor Sandro Remo Martins Neves Ramos Freitas

Dissertação elaborada com vista à obtenção do Grau de Doutor no ramo Motricidade Humana, na especialidade de Comportamento Motor
Tese por compilação de artigos, realizada ao abrigo da alínea a) do nº2 do artº 31º do Decreto-Lei º 230/2009

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Título da Tese: Effects of neural tension in the sciatic nerve stiffness, in healthy people and people with low back related leg pain

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Faculdade de Motricidade Humana – Universidade de Lisboa
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Assinatura:____________________________
(Tiago Gonçalves Neto)

DEDICATÓRIA

Para a minha família

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O doutoramento é um processo composto por diferentes capítulos, assemelhando-se a uma história. E para esta história importam não apenas os métodos e técnicas que se desenvolvem, os equipamentos que se aprende a dominar, ou os laboratórios que servem como segunda casa, mas importam sobretudo as pessoas que se conhece e que dão significado a toda esta história. Mais que um acto de obrigação ou dever, estas linhas expressam um profundo reconhecimento da importância que essas pessoas tiveram durante este doutoramento.

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TITULO: Efeitos da tensão neural na rigidez do nervo ciático, em pessoas saudáveis e em pessoas com dor lombar dor irradiada para o membro inferior

RESUMO

As manobras de neurodinâmica são utilizadas no âmbito clínico como forma de avaliação dos nervos periféricos, bem como de intervenção em patologias que afectam o quadrante inferior (e.g. dor lombar irradiada para o membro inferior - DLIMI), e ainda como treino de flexibilidade em populações saudáveis. Contudo, não existe evidência suficiente sobre os efeitos clínicos e mecânicos das manobras de neurodinâmica, nomeadamente das de tensão neural, dirigidas ao quadrante inferior. Assim, o objectivo principal desta tese foi determinar os efeitos agudos de uma técnica de tensão neural na rigidez do nervo ciático, estimada por elastografia de *shear wave*, em pessoas saudáveis e em pessoas com DLIMI. Para tal, três estudos foram realizados: 1) Uma revisão sistemática, com meta-análise, que demonstrou elevada evidência das manobras de neurodinâmica no alívio da dor e melhoria da incapacidade em pessoas com lombalgia, bem como evidência moderada no aumento da flexibilidade em pessoas saudáveis; 2) Um estudo em sujeitos saudáveis e sem história de dor lombar que revelou ausência de efeitos imediatos significativos da aplicação de tensão neural na posição de *slump* na redução da rigidez do nervo ciático; 3) Um estudo onde se verificou que pessoas com DLIMI apresentaram uma rigidez do nervo ciático mais elevada no membro afectado comparativamente ao não afectado, e a controlos saudáveis; e que uma técnica de tensão neural permitiu restabelecer a simetria de rigidez do nervo ciático entre membros. Estes resultados evidenciam os efeitos clínicos e mecânicos das manobras de neurodinâmica, nomeadamente de tensão neural. Os efeitos da tensão neural na redução da rigidez do nervo ciático em pessoas com DLIMI parecem estar relacionados com alterações nas propriedades mecânicas do nervo. No entanto, investigações futuras deverão confirmar esta hipótese, bem como analisar os efeitos a médio e longo prazo das manobras de neurodinâmica sobre as propriedades mecânicas do nervo ciático.

PALAVRAS-CHAVE: Nervo ciático; Neurodinâmica; *Slump*; Lombalgia; Velocidade de ondas de corte mecânicas; Elastografia

TITTLE: Effects of neural tension in the sciatic nerve stiffness, in healthy people and people with low back related leg pain

ABSTRACT

Neurodynamics techniques, such as neural tension maneuvers, are often used by health professionals to assess the peripheral nerves properties. They are also used in the rehabilitation of several lower body quadrant disorders (i.e. as in low back related leg pain – LBRLP), or as a training method in healthy individuals. Nevertheless, there is insufficient evidence of the neurodynamics effects, mainly neural tension, when applied to the lower body quadrant. This thesis aimed to determine the immediate effects of neural tension in the sciatic nerve stiffness, estimated by shear wave elastography, in both healthy people and people with LBRLP. Three studies were conducted to meet with this purpose: 1) a systematic review, with meta-analysis, which revealed evidence favoring the use of neurodynamics techniques for pain relief and disability improvement in people with low back pain, and for flexibility improvements in healthy people; 2) a study that showed no significant effects of neural tension in a slump position in reducing the sciatic nerve stiffness of healthy people; and 3) a study which determined that people with LBRLP present greater sciatic nerve stiffness in the affected limb compared to the unaffected limb, and to healthy controls; and that neural tension immediatly reduced the sciatic nerve stiffness of the affected limb. This thesis provides evidence of the clinical and mechanical effects of neurodynamics techniques, mainly neural stiffness. The effect of neural tension in reducing the sciatic stiffness in people with LBRLP seems to be related with changes in the nerve mechanical properties, however future research should confirm this finding while also determining the long-term effects of neurodynamics techniques.

KEYWORDS: Sciatic nerve; Neurodynamics; Slump; Low back pain; Shear wave velocity; Elastography

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LIST OF ABBREVIATIONS

AKE – Active Knee Extension Test
BMI – Body Mass Index
CI – Confidence intervals
CSA – Cross Sectional Area
CTS – Carpal Tunnel Syndrome
CV – Coefficient of Variation
EMG – Electromyography
ICC – Intraclass Correlation Coefficient
LBP – Low Back Pain
LBRLP – Low Back Related Leg Pain
MDD – Minimal Detectable Difference
MIVC – Maximal Isometric Voluntary Contraction
NM – Neural Mobilization
ODI – Oswestry Disability Index
RCT – Randomized Controlled Trials
ROM – Range of Motion
RMDQ – Roland Morris Disability Questionnaire
SD – Standard Deviation
SEM – Standard Error of Measurement
SLR – Straight Leg Raise
SWE – Shear Wave Elastography
SWV – Shear Wave Velocity
SSI – Supersonic Shear Imaging
ULTT – Upper Limb Tension Test
US – Ultrasonography/Ultrasonographic/Ultrasound
VAS – Visual Analogic Scale

CHAPTER I - Introduction

Neurodynamics techniques are frequently used to evaluate the peripheral nerves (Shacklock, 1995), both in the upper and the lower body quadrant. Neurodynamics uses a combination of movements that gradually load the peripheral nerve until the subject reaches his maximal range of motion (ROM) (Butler, 2000) in order to assess the nerve mechanosensitivity (Boyd, Wanek, Gray, & Topp, 2009).

Besides being used as an assessment tool, neurodynamics techniques, which can be grouped as neural tension, or neural gliding techniques (Shacklock, 1995), are also used with a rehabilitation purpose (e.g. in people with peripheral neuropathy) (Oskay et al., 2010), and as a training method in healthy people (e.g. for flexibility improvements) (Castellote-Caballero, Valenza, Puentedura, Fernández-de-Las-Peñas, & Alburquerque-Sendín, 2014). In the past years, a considerable number of studies have been published reporting the effects of neurodynamics interventions (Kitteringham & Christine, 1996; Scrimshaw & Maher, 2001; Tal-Akabi & Rushton, 2000).

While the majority of the studies using neurodynamics techniques aimed at the upper body quadrant report positive effects (Akalin et al., 2002; Coppieters, Stappaerts, Wouters, & Janssens, 2003; Nee, Vicenzino, Jull, Cleland, & Coppieters, 2012), the same has not been reported for the lower body quadrant. The reasons for this lack of evidence are related to the few number of studies, and also to conflicting results. Some studies report effects of neurodynamics techniques superior to the control, or minimal interventions, in both healthy (Castellote-Caballero et al., 2014) and clinical populations (i.e. mainly in people with low back pain - LBP) (Cleland, Childs, Palmer, & Eberhart, 2006; Nagrale, Patil, Gandhi, & Learman, 2012). On the other hand, some studies concluded that neurodynamics interventions were not superior to the control, or minimal interventions, in both populations (Scrimshaw & Maher, 2001; Webright, Randolph, & Perrin, 1997).

Thus, it is important to determine the evidence associated with the effects of neurodynamics techniques applied to the lower body quadrant, in either healthy individuals or clinical populations, particularly people with LBP, which is one of the most common problems affecting the lower body quadrant (Hoy et al., 2012).

In addition there is also a lack of knowledge surrounding the mechanical and physiological effects that neurodynamics, mainly neural tension, immediately produces following its application. Several theories can be found in the literature related, for instance, to pain mechanisms (Dilley, Lynn, & Pang, 2005) or to intraneural fluid dispersion (Gilbert et al., 2015). However, these are mere hypothesis driven by investigations in human cadavers or in animal models. There are few studies that analyze, *in vivo,* the acute effects of neurodynamics maneuvers. In the recent years the mechanical properties of the peripheral nerves (e.g. neural strain, or excursion) have been fairly examined, mostly in animal models (Mason & Phillips, 2011; Phillips, Smit, De Zoysa, Afoke, & Brown, 2004) and in human cadavers (Boyd, Topp, & Coppieters, 2013; Coppieters et al., 2006), but also using ultrasonography (US) brightness-mode imaging (Carroll, Matthew, Janet, Keith, & Wayne, 2012; Hough, Moore, & Jones, 2000). In fact, US allows to measure peripheral nerves' morphology [e.g. cross-sectional area (CSA)] (Bathala, Kumar, Kumar, Shaik, & Visser, 2014), and to quantify neural excursion in different planes (Ellis, Hing, Dilley, & McNair, 2008), but these studies fail to provide direct evidence about the nature and magnitude of the forces that act upon the human peripheral nerves. This has recently been possible, since shear wave elastography (SWE) was developed. This technique measures shear wave velocity (SWV) within soft tissues, which in turn corresponds to the tissues' shear modulus (Drakonaki, Allen, & Wilson, 2012). Briefly, SWE transmits ultrasound waves to interact with the tissues. In response, shear waves will be produced, and their velocity can be measured and used to estimate the stiffness of tissues (Bercoff, Tanter, & Fink, 2004). Recently, SWE was used with the objective of estimate the stiffness of peripheral nerves, such as the median (Kantarci et al., 2014), tibial (Greening & Dilley, 2016), and sciatic (Andrade et al., 2016) nerves. Moderate (Greening & Dilley, 2016) to excellent (Andrade et al., 2016) reliability values have been reported for SWV measurements, which support the use of this method to assess the mechanical properties of peripheral nerves. Consequently, it would be relevant to use SWE to determine the acute effects of neural tension in the stiffness of the sciatic nerve, both in healthy and clinical populations.

Additionally, SWE has also been used to estimate the stiffness of nerves in people with several neuropathies, such as carpal tunnel syndrome (Kantarci et al., 2014), or diabetic neuropathy (Dikici et al., 2016). Yet, there is no information about the stiffness of the sciatic nerve in people with low back related leg pain (LBRLP), often termed *sciatica*, a very common neuromuscular disorder that reaches lifetime prevalence rates up to 43% (Konstantinou & Dunn, 2008). Hence, it would be important to determine if there are changes in the sciatic nerve stiffness in people with LBRLP.

Objectives and Hypothesis

The **main purpose** of this thesis was to investigate the immediate changes to sciatic nerve stiffness after a slump mobilisation technique in healthy participants and in those with LBRLP. In order to reach this primary objective, three studies were carried out, each one with its specific goals, but all following a logic sequence, and dependent from each other.

The **study 1** was conducted with the objectives of:

1) Systematically evaluate the current body of evidence into the effectiveness of neurodynamic mobilizations applied to the lower body quadrant, in healthy people and in people with LBP;

2) Determine the most used parameters for neurodynamics protocols.

In order to meet with these purposes we performed a systematic review, with meta-analysis, of the effects of neurodynamics in healthy individuals and in people with LBP. Considering the lack of evidence regarding the effects of neurodyanimcs, in particular targeting the lower body quadrant, we searched the literature for randomized controlled trials (RCT) which used any form of neurodynamics aimed to the lower body quadrant. We also used the systematic review to determine the most used parameters in neurodynamics interventions, related for instance with the number and frequency of sessions, duration of the intervention, and type of technique used. This information was later used in the second study to establish the experimental protocol.

The hypothesis formulated for this first study was that the meta-analysis would yield significant effect sizes favoring the use of neurodynamics techniques in both healthy individuals and in people with LBP.

The **study 2** was performed to meet with the following objectives:

1) To determine the immediate effects of a slump mobilization technique in the sciatic nerve stiffness of healthy individuals;
2) To ascertain the reproducibility of the sciatic stiffness assessments;
3) To establish the reliability of the experimental setup in order to replicate it in clinical populations

This second study had a quasi-experimental design, and it was conducted in healthy participants. Considering the lack of knowledge regarding the mechanical effects of neurodynamics techniques in human nerves, we measured the sciatic nerve stiffness (i.e. estimated through the measurement of SWV) before, and immediately after, a neural tension intervention. The parameters of the neural tension intervention were selected accordingly to the findings of the study 1. Consequently, a sustained slump position was used to induce neural tension in the sciatic nerve. In addition, reproducibility of the measurements was determined by performing two SWV assessments (1 min between measurements) in each limb.

The following hypotheses were tested in this study:

a) A sustained slump position would lead to an acute decrease in the sciatic nerve stiffness, in healthy participants;
b) The measurements of SWE would yield substantial intra-rater reproducibility

, Finally, the **study 3** aimed to address the following objectives:

1) To measure the sciatic nerve stiffness in people with unilateral LBRLP, and compare it between limbs;
2) To compare the sciatic nerve stiffness between healthy individuals and people with LBRLP;
3) To determine the acute effects of neural tension in the sciatic nerve stiffness of people with LBRLP

Similarly to the second study, this one was also a quasi-experimental study. Given that the literature shows changes to the median and tibial nerves stiffness as a consequence of several neuropathies, this study intended to analyze if the sciatic nerve stiffness was also altered in people with unilateral LBRLP. The experimental protocol used and validated in the second study for the sciatic SWV assessment was replicated in this one. Moreover, the acute effects of neural tension were also determined in this population, being the affected limb subjected to the intervention, while the unaffected limb served as control.

Three hypotheses were formulated for this study, as follows:

a) The affected limb of people with unilateral LBRLP would present higher stiffness than the unaffected limb;
b) The affected limb of people with unilateral LBRLP would present higher stiffness when compared to either limb of healthy controls;
c) A neural tension intervention would lead to an acute decrease in the sciatic nerve stiffness, in people with LBRLP.

Structure of the thesis

This thesis follows a study compilation organization, and is presented as follows:

- Chapter I, shows a Introduction, where the problem of the investigation is identified, and the objectives are presented;
- Chapter II, shows a Review of the Literature, where the main concepts are defined and explained. The topics related to the neurodynamics, peripheral nervous system, and shear wave elastography are explored and detailed to the reader;
- Chapters III to V, show, respectively, the three studies mentioned above. These chapters share the same organization: Introduction, Methods, Results, Discussion, Conclusions, and References;
- Chapter VI and VII, shows the General Discussion and Conclusions, respectively, where we establish a link between the 3 studies presented, and the Introduction. A summary of the main findings observed in the studies is performed, followed by a rationale of how these results can be useful for clinicians in their practice. The limitations of the thesis are also discussed in this chapter, as well as the recommendations for future research. The final considerations regarding this thesis are presented in the Conclusions section;
- And, Chapter VIII, which represents the list of References used in the chapters I, II, and VI. This chapter does not include the references used in the studies, given that each one of them has its own reference list.

CHAPTER II - Review of the Literature

1. Peripheral nerve anatomy

Peripheral nerves have a fascicular organization, meaning that axons are bundled together along the nerve's length (Topp & Boyd, 2012). Protecting the nerve there are 3 different layers of connective tissue: the endoneurium, the perineurium, and the epineurium (Topp & Boyd, 2006). The endoneurium is the innermost connective tissue, and is found between individual nerve fibers; the perineurium bundles nerve fibers into a fascicle, and provides mechanical strength to the nerve, being reinforced where the nerve crosses joints (Lowry, Wilcox, Masson, & Williams, 1997); the epineurium is the outermost layer, and holds fascicles together to form a nerve trunk. When the nerve has more than one fascicle the epineurium is divided into epifascicular and interfascicular (Stolinski, 1995). The first forms an interface between the nerve and their surrounding tissues, whereas the interfascicular epineurium allows gliding between nerve fascicles (Stolinski, 1995).

The blood supply to the peripheral nerves is assured by arterioles and venules that run across the length of the nerve, within the epineurial space (Olsson, 1990). From here, the vessels pass obliquely into the perineurial compartment, transporting perineural cells (Olsson, 1990). The amount of blood vessels is not similar throughout the nerve. The density of capillaries is higher in the regions with larger metabolic needs, such as the dorsal root ganglia, and smaller in the endoneurial space of the peripheral nerve (Bell & Weddell, 1984).

The interface formed between the blood vessels and the nerve, known as the blood-nerve barrier, is of major importance. Intact endoneurial capillaries help to regulate an adequate intraneural pressure, counteracting the oncotic pressure from surrounding tissues (Sunderland, 1978). If this equilibrium is compromised, changes to intraneural blood flow will occur, causing for instance ischemia, or an accumulation of intraneural fluid, which will be difficult to drain since there are no lymphatic capillaries in the endoneurial compartment (Sunderland, 1978).

1.1. Sciatic nerve anatomy

The sciatic nerve has its origin in the sacral plexus. The sacral plexus is formed by the lumbo-sacral cord, and the anterior divisions of the 3 upper sacral nerves. The upper nerves of the plexus (i.e. lumbo-sacral cord, the 2 first, and part of the third, sacral nerves) will prolong into the sciatic nerve. This nerve will leave the pelvis through the great sacro-sciatic foramen, traveling along the posterior thigh covered by the long head of the biceps femoris. When the sciatic reaches the lower third of the thigh it divides into the external popliteal nerve and the internal popliteal nerve, which will distally continue as the tibial nerve (Gray, 1977). The sciatic has numerous branches responsible for innervating most of the articular and muscular structures of the lower limb, and also for the cutaneous innervation of the leg and foot (VanPutte et al., 2013). The path and territory innervated by the sciatic is directly related to the symptomatology of the people with LBRLP, which will be later described.

2. Peripheral nerves biomechanics

Peripheral nerves exhibit some biomechanical properties which enables them to withstand various mechanical stresses, imposed during joint movement (Topp & Boyd, 2006). Nerves have the ability to glide (or slide) relatively to the surrounding tissues. That ability is termed excursion, and its direction varies accordingly to the axis of rotation in the moving joint (Dilley, Lynn, Greening, & DeLeon, 2003). The nerve glides towards the moving joint (i.e. convergence) when there is elongation of the nerve bed; on the other end, when tension is released from the nerve bed the nerve will glide away from the moving joint (i.e. divergence) (Wright, Glowczewskie, Cowin, & Wheeler, 2001). Neural excursion occurs first in the segments adjacent to the moving joint, and progress distally to the axis of rotation (Wright et al., 2001). Similarly, excursion levels are greater in the adjacent segments when compared to the segments distal to the moving joint (Boyd, Puttlitz, Gan, & Topp, 2005).

Joint movement not only produces neural excursion, but also causes changes in neural strain, i.e. nerve deformation caused by longitudinal stress (Driscoll, Glasby, & Lawson, 2002). Nerves subjected to tensile stresses show a strain increase, which can be described in a stress-strain curve. The first phase of the curve is characterized by a toe region, representing the straightening of the wavy neural connective tissues following minimal stress. With gradual stress increase, neural strain will grow at a steady rate until ultimate strain is reached, causing permanent nerve deformation (Kwan, Wall, Massie, & Garfin, 1992). The slope of the stress-strain curve indicates the resistance of the nerve to deformation, known as stiffness (Topp & Boyd, 2006). Increasing neural strain will cause a phenomenon known as *transverse contraction,* which is a reduction in the nerve's cross-sectional area. This results in an increase of the intraneural pressure (Millesi, Zöch, & Reihsner, 1995).

Neural excursion, strain, and stiffness are not homogeneous throughout the nerve's length. An animal study analyzed the local variations in mechanical properties of the median and sciatic nerve. The authors found that both nerves show greater strain in the joint regions, while stiffness values were significantly smaller, compared to the non-joint regions (Phillips et al., 2004). In addition, it is known that nerve stiffness is dependent from the elongation velocity (Driscoll et al., 2002), which is consistent with a viscoelastic and time-dependent behavior. As seen in the muscle-tendon unit (Kubo, Kanehisa, & Fukunaga, 2002; Magnusson, Simonsen, Aagaard, & Kjaer, 1996; Mizuno, Matsumoto, & Umemura, 2013), nerves also present stress relaxation and creep (Driscoll et al., 2002). This means that when nerves are stretched and maintained in an elongated position, their stiffness will decrease, and their length will increase. Interestingly, it was found, in animals, that stress relaxation is greater when smaller elongation rates are applied, and when performed at slower velocities. However, we must take into consideration that these findings were mostly observed in animal studies, and in cadaveric investigations. The living tissues surrounding peripheral nerves may have a strong influence on the nerve biomechanics, and more information from studies *in vivo* is necessary.

2.1. Biomechanics of the sciatic nerve in people with low back related leg pain

Low back pain is one of the most common musculoskeletal disorders, with lifetime prevalence over 70% (Burton et al., 2006). It is defined as the presence of pain and discomfort below the costal margin and above the gluteal fold (Koes, 2006). Frequently, LBP is accompanied by irradiating symptoms, such as pain or numbness, along the regions innervated by the sciatic nerve and their nerve roots, which is characteristic of LBRLP (Bogduk, 2009). Several conditions are linked with the development of radicular symptoms, mainly herniated disks, but also spinal stenosis, spondylolisthesis (Schoenfeld, Laughlin, Bader, & Bono, 2012), or nerve root inflammation (Bogduk, 2009). Low back related leg pain is usually unilateral, and involves irradiating pain that travels dorsolaterally in the thigh when there is compression of the L5 nerve root, and posteriorly when the S1 nerve root is compressed. Pain is anterolateral in the thigh following L4 nerve root compression (Ropper & Zafonte, 2015). Additionally, muscle weakness and reflex changes may also be present in lumbar radiculopathies, mainly in L4/L5 nerve roots compression (Konstantinou & Dunn, 2008).

Information is scarce concerning the mechanical behaviour of the peripheral nerves in people with LBRLP. Recently, studies analysing people with unilateral radiculopathy have observed an increased cross-sectional area of the affected sciatic nerve in comparison to the unaffected sciatic (Frost & Brown, 2016; Kara et al., 2012). Another study showed that the transverse displacement direction of the sciatic nerve was altered in people with LBRLP (Ridehalgh, Moore, & Hough, 2015). Despite these changes found, it is unknown to this date, if the sciatic nerve in people with LBRLP has any change to its mechanical properties, mainly stiffness.

Next, we will characterize the neurodynamics techniques, which are amongst the most used interventions to evaluate and treat people with LBRLP. Its various effects on the peripheral nerves will also be presented.

3. Neurodynamics: Definition and types of techniques

The nervous system has mechanical and physiological functions which interact closely, being dynamically interdependent. The concept of Neurodynamics joins the mechanical and the physiological components of the nervous system (Shacklock, 1995). A change in one or in both functions will cause impairment for proper neurodynamics (Shacklock, 2014). For instance, inadequate and constant mechanical stresses (e.g. excessive strain, or compressive forces) applied to the peripheral nerves will result in intraneural blood flow changes, inflammation, and mechanosensitivity (Shacklock, 2014). On the other hand, physiological changes as the one seen in diabetic patients that develop distal symmetric polyneuropathy, causes an increase in the nerve's CSA, which will compromise its mechanical properties (i.e. longitudinal excursion) (Boyd & Andrew, 2014).

Neurodynamics interventions include several techniques used for assessment and treatment of peripheral nervous system related problems (Butler, 2000). These techniques use a combination of joint movements in order to promote neural gliding and neural tension. Exercises aimed for neural gliding induce excursion of the nerve relative to its surrounding structures, by elongating the nerve bed at one end and reducing it at the other end; neural tension exercises promote nerve elongation at both ends, which results in an increase of neural strain (Coppieters & Butler, 2008).

The most common neurodynamics techniques for the upper body quadrant include the Upper Limb Tension tests, which target the peripheral nerves from the brachial plexus (e.g. median, ulnar, or radial nerves) (Kleinrensink et al., 2000). Regarding the lower body quadrant, the Straight Leg Raise (SLR) test, and the Slump test, are the most common techniques applied. The SLR test consists in a passive hip flexion movement, while the knee remains in full extension, performed in supine (Breig & Troup, 1979). This test is traditionally applied to evaluate lumbosacral nerve roots disorders, with some variations being used as sensitizing, or differentiation, maneuvers (e.g. medial hip rotation, or ankle dorsiflexion) to distinguish the symptoms originated in neural and non-neural structures (Boyd et al., 2009).

The slump test is used to determine the relationship between the patient's symptoms and the restriction of movement of the pain-sensitive structures (Maitland, 1979). During this test, patients are seated with the thoracolumbar spine in a slump position, and the cervical spine flexed. Afterwards, knee extension and ankle dorsiflexion are performed, adding additional mechanical stress to the nervous system. Finally, cervical extension is performed as a differentiation maneuver (Maitland, 1985). Some variations of the slump test are described, by changing the test order (Miller, 1999): ankle dorsiflexion may be applied prior to knee extension, and a "long-sitting" position may be considered to initiate the slump test sequence.

The slump test position is also used to apply neurodynamics techniques. Some studies use a sustained slump test position to induce neural tension (Cleland et al., 2006; Nagrale et al., 2012). In this case, cervical flexion is maintained during the period of intervention, while the ankle is maximally dorsiflexed by the examiner (Cleland et al., 2006). Neural gliding exercises are also performed in a slump position (Castellote-Caballero et al., 2013). While maintaining the thoracolumbar spine slumped, patients are instructed to alternate cervical with knee movements (Sharma, Balthillaya, Rao, & Mani, 2016). The combination of cervical extension with knee extension will cause a distal excursion of the sciatic, whereas proximal neural excursion occurs during cervical flexion/knee flexion (Ellis, Hing, & McNair, 2012).

4. Effects of Neurodynamics

The effects of neurodynamics are reported in the literature both in clinical (Colakovic & Avdic, 2013; Scrimshaw & Maher, 2001) and healthy populations (Méndez-Sánchez et al., 2010; Sharma et al., 2016). This means that these techniques are used either to rehabilitate neuromuscular disorders (Allison, Nagy, & Hall, 2002; Cleland et al., 2006), or to enhance physical performance, like joint flexibility (Castellote-Caballero et al., 2013). A systematic review determined that 8 out of 11 studies reported positive effects from the use of neurodynamics, mostly in upper body quadrant disorders (Ellis & Hing, 2008). More recently, a meta-analysis determined moderate and large effect sizes favoring the use of neurodynamics techniques in pain relief and disability improvements, respectively (Su & Lim, 2015). Again, these findings were mostly retrieved from studies in the upper body quadrant.

As with clinical populations, the effects of neurodynamics in healthy individuals are positive, resulting in acute lower limb flexibility improvements (Sharma et al., 2016), even when compared to performing static stretching, a method with well-known results in increasing flexibility (Castellote-Caballero et al., 2014; Méndez-Sánchez et al., 2010).

The reasons for the clinical effects of neurodynamics in pain and disability, and in flexibility, are not entirely known. Several physiological and mechanical explanations are proposed, that will be detailed.

4.1. Effects on blood flow

As discussed earlier, the peripheral nerves have a network of blood vessels present in every layer of its fascicular organization. When a longitudinal force is applied to the nerve, it will begin to elongate and to strain. Consequently, the blood vessels will also elongate (Shacklock, 1995). This happens within a physiological range (i.e. 6% to 8%), during joint motion (Topp & Boyd, 2006). Animal studies showed that with 8% strain venous return starts to decline, and by 15% there is a complete occlusion in blood flow (Lundborg & Rydevik, 1973; Ogata & Naito, 1986). In addition, data from a cadaveric study revealed that a position similar to the upper limb tension test for the median nerve (i.e. shoulder abduction and external rotation + forearm supination + elbow, wrist, and fingers extension) resulted in 7.6 ± 8.2 % strain in the median nerve (Byl, Puttlitz, Byl, Lotz, & Topp, 2002). The same position, but using elbow flexion and forearm pronation, resulted in strain levels of 9.9 ± 10.9 % for the ulnar nerve (Byl et al., 2002). Similar strain values were found for the sciatic nerve, during the SLR maneuver in human cadavers (Coppieters et al., 2006).

Apparently, these strain values may be superior to the ones indicated for total blood flow occlusion. Following a constant compressive or tensile force applied to the nerve, the resulting blood flow restriction may cause endoneurial edema and fibrosis (Rydevik & Lundborg, 1977).

Accordingly to Wang et al. (2015), neurodynamics favors peripheral nerve regeneration. These techniques facilitate intraneural blood flow, which will improve the availability of oxygen and nutrients to the neural tissue (Wang et al., 2015). Previously to this investigation, a cadaveric study described the effects of neural mobilization as a *"pumping action"* (Brown et al., 2011). In this study, Brown et al (2011) used repetitive passive ankle mobilization, which caused an intermittent change in the tibial nerve internal pressure (Brown et al., 2011). This pumping effect may have a direct influence on intraneural blood flow, favoring fluid dispersion, thereby preventing the deposition of mechanosensitivity elements (Brown et al., 2011).

4.2. Effects on pain/mechanosensitivity

Mechanosensitivity is defined as the generation of pain impulses as a consequence of mechanical stimulus (e.g. compressive or tensile stresses) applied to neural structures (Shacklock, 1995). It can affect both myelinated and unmyelinated fibers (Dilley et al., 2005), and is caused by the accumulation of mechanically sensitive elements (e.g. colchicine). This leads to a disruption in axoplasmic transport (Dilley & Bove, 2008), and consequently to the development of local mechanosensitivity.
Neurodynamics maneuvers aim to assess the mechanosensitivity associated with range of motion restriction (Butler, 2000), that was recently found in patients with CTS (Jaberzadeh & Zoghi, 2013) and diabetic polyneuropathy (Boyd, Wanek, Gray, & Topp, 2010). Consequently, neurodynamics interventions have the purpose of restoring normal nerve mechanosensitivity, enabling pain free ROM. Several studies report positive effects of neurodynamics techniques on pain relief, either in upper body (Colakovic & Avdic, 2013; Nee et al., 2012; Pinar, Enhos, Ada, & Güngör, 2005), or lower body (Nagrale et al., 2012) quadrant disorders. The physiological reasons for this benefit of neurodynamics are probably related with hypoalgesic effects, already shown in healthy subjects (Beltran-Alacreu, Jiménez-Sanz, Fernández Carnero, & La Touche, 2015). Beltran et al. (2015) compared the immediate mechanical hypoalgesic effects of neurodynamics, with a placebo intervention, in healthy individuals. They found an immediate widespread hypoalgesic effect, following 7 min of neural gliding or neural tensioning maneuvers (Beltran-Alacreu et al., 2015). A recent study, in animals, also showed the effect of neurodynamics techniques in reducing hyperalgesia (Santos et al., 2012). This effect on pain sensation is probably a consequence of an inhibition of temporal summation, as a result of central sensitization in the dorsal horn of the spinal cord (Staud, Price, Robinson, Mauderli, & Vierck, 2004; Woolf, 2011)

4.3. Mechanical effects

As described earlier, peripheral nerves exhibit viscoelastic properties which enable them to glide and elongate, in order to adapt to human movement (Topp & Boyd, 2006). These characteristics have been extensively studied in animal (Kwan et al., 1992; Mason & Phillips, 2011; Wall, Kwan, Rydevik, Woo, & Garfin, 1991) and cadaveric (Boyd et al., 2013; Byl et al., 2002) research, but only recently studies *in vivo* analyzed neural excursion and strain of the peripheral nerves (Carroll et al., 2012; Coppieters, Hough, & Dilley, 2009; Shum, Attenborough, Marsden, & Hough, 2013). A recent systematic review (Silva et al., 2014) analyzed studies *in vivo* that quantified neural excursion and strain. It was concluded that the sciatic nerve has, in average, 3.5 mm of longitudinal excursion, when alternate movements are used in the cervical spine and knee joint, in a slump position. These results are quite different from the ones determined in cadaveric studies, where values up to 28 mm (Coppieters et al., 2006) are reported. This illustrates the influence that the tissues surrounding the nerves have on their mechanical properties.

One of the main objectives in using neurodynamics is to restore proper nerve biomechanics (Butler, 2000), despite the lack of evidence of such effect. Literature shows that peripheral nerves mechanical properties are altered in some pathological conditions. It was determined that patients with carpal tunnel syndrome have a reduction of the longitudinal excursion in the median nerve, when compared to healthy controls (Hough, Moore, & Jones, 2007). In addition, it was also found that the median nerve CSA (Lopes, Lawson, Scott, & Keir, 2011) was increased, and its transverse movement was reduced (van Doesburg, Henderson, Mink van der Molen, An, & Amadio, 2012), in people with CTS.

Regarding the lower body quadrant, the sciatic nerve showed less transverse movement, but not longitudinal, in people with spinally referred leg pain (Ridehalgh et al., 2015), while the tibial nerve presented an increased CSA and smaller longitudinal excursion, in people with diabetic polyneuropathy (Boyd & Andrew, 2014).

To date, we know of no studies that assessed the long-term effects of a neurodynamics intervention on the restoration of altered nerve biomechanics. Nevertheless, the immediate impact of neurodynamics on the excursion and strain is known, as well as the influence of the movement sequence during the technique (Boyd et al., 2013; Nee, Yang, Liang, Tseng, & Coppieters, 2010). Using human cadavers, Boyd et al (2013) studied 2 sequences of SLR: a) performing the SLR maneuver with hip flexion followed by ankle dorsiflexion; and b) invert the sequence, performing ankle dorsiflexion before hip flexion. It was observed that, at the knee region, there were no differences between the 2 sequences in maximal strain or excursion of the sciatic nerve. Additionally, it was found that strain and excursion increased earlier, and maintained increased for longer periods, in the regions closest to the moving joint (Boyd et al., 2013). This follows the convergence phenomenon referred earlier, where a nerve under tensile stress tends to glide towards the moving joint (Wright et al., 2001).

Another important finding is related with the technique that allows for greater neural excursion. Ellis et al (2012) compared the effects of different neurodynamics techniques (Fig.1.), performed in a slump position, in the sciatic nerve excursion. The *"slider"* technique (i.e. alternating cervical with knee movement – Fig.1. – A) showed higher excursion values (i.e. 3.2 mm), compared to a tension technique (Fig. 1. – D) or to a single-joint slider technique (Fig. 1. – B and C) (Ellis et al., 2012).

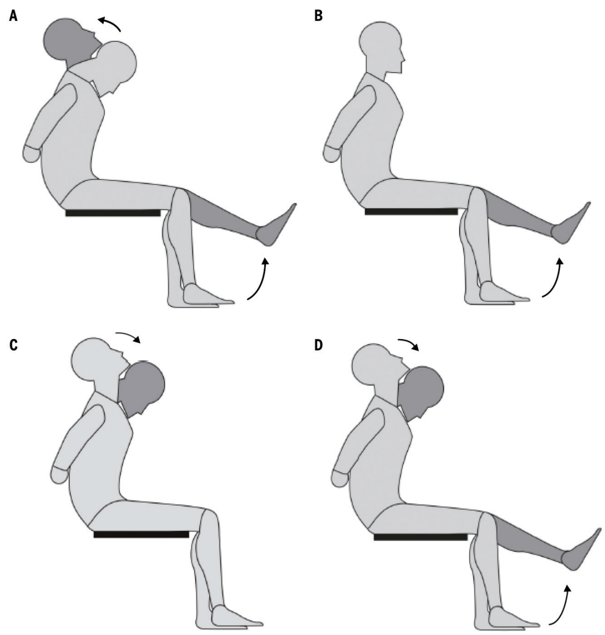

Figure 1. Four examples of neurodynamics techniques used in a slump position: A – slider technique, alternating cervical movement with knee movement; B – single joint slider technique (knee); C – single joint slider technique (cervical); D – tensioner technique. Image retrieved from Ellis et al. (2012).

These findings are relevant to a clinical context given that provide valuable information regarding the neurodynamics parameters which have more impact on the nerve biomechanics. However, information is still scarce concerning the magnitude and effect of the forces (e.g. stiffness) transmitted to the neural tissue during and after neurodynamics techniques.

5. Ultrasonography in the assessment of peripheral nerves characteristics

Ultrasonographic imaging made it possible to measure *in vivo* the motion of soft tissues, in alternative to more expensive technologies such as magnetic resonance imaging (Hough et al., 2000). Using the brightness mode (i.e. B-mode) it is possible to have a continuous real-time image, displayed in a grey-scale image (Dilley, Greening, Lynn, Leary, & Morris, 2001). By comparing two consecutive images, distances and displacements between structures can be determined (Hough et al., 2000). This method was used by Fukunaga et al (1996) to measure the tendinous movement of the tibialis anterior muscle during voluntary contractions (Fukunaga et al., 1996). With a similar method the transverse motion of the median nerve was also measured (Nakamichi & Tachibana, 1992). However, the longitudinal motion of peripheral nerves only became possible to be determined with the advances in speckle tracking. This method recognizes and tracks two different points in the B-mode picture (Meunier, 1998), enabling to quantify their displacement in two consecutive images (Anderson & McDicken, 1999). Another important development to assess nerve excursion was the frame-by-frame cross correlation method (Dilley et al., 2001). Dilley et al (2001) developed an algorithm which quantifies the motion between the selected regions of interest, in two consecutive frames of the image sequence (Dilley et al., 2001).

The combination of high-frequency US imaging with the cross correlation analysis, allowed the estimation *in vivo* of the longitudinal nerve excursion. Neurodynamics studies benefited from these technological advances, as it became possible to analyse neural biomechanics during neurodynamics techniques, such as the ULTT (Coppieters & Butler, 2008), SLR (Ridehalgh, Moore, & Hough, 2012), or Slump tests (Ellis et al., 2012). It also allowed to characterize, from a biomechanical point of view, the peripheral nerves affected by some of the most common neuropathies (Boyd & Andrew, 2014; Ridehalgh et al., 2015).

Although studies using US to measure nerve dynamics represented important information for clinicians and researchers, there are limitations associated with this method, specifically when it comes to infer about nerve stiffness. Considering a nerve being elongated in its slack length, the excursion will be considerable, while little change occurs in stiffness (Andrade et al., 2016). Thus, it is important to understand *in vivo* the effects of joint motion in neural stiffness, which only recently has been possible due to SWE.

6. Elastography and the advances in measuring the stiffness of soft tissues

Elastography is a technique developed over the past 20 years, that allows to estimate the Young's modulus which is the physical parameter equivalent to stiffness (Gennisson, Deffieux, Fink, & Tanter, 2013). This technology has been in constant improvement with the purpose of providing faster analysis at higher resolutions. Quasi-static elastography methods (e.g. strain elastography) were initially used to assess soft tissues stiffness, by applying a constant compressive force to superficial tissues (Drakonaki et al., 2012). This method has some disadvantages such as being unable to quantify the stiffness because the applied stress distribution is unknown (Brandenburg et al., 2014). In addition, strain elastography is limited to the superficial tissues given that the stress applied is operator dependent (Gennisson et al., 2013).

Instead of using an external compressive force, acoustic radiation force impulses is another elastography method that estimates the stiffness of tissues by using one focalised US beam that will cause tissue displacement (Drakonaki et al., 2012). The transducer will detect and follow the resultant displacement (i.e. by speckle tracking), allowing the reconstruction qualitative maps of tissue stiffness (Gennisson et al., 2013). Although this method is more reliable than strain elastography, and allows for the assessment of deeper tissues, it still does not provide quantitative data on tissue stiffness (Brandenburg et al., 2014).

6.1. Shear wave elastography

Shear wave elastography is a method that enables to quantitatively measure tissue stiffness (Bercoff et al., 2004). Shear waves are the product of tissue displacement following US push beams (Brandenburg et al., 2014; Drakonaki et al., 2012), and their velocity is correlated with the stiffness of tissues (Brandenburg et al., 2014).

Supersonic shear imaging (SSI) is perhaps the state of the art of SWE techniques. Developed by the Institute Langevin SSI uses ultrafast imaging (i.e. up to 30.000 images per second) to obtain a full acquisition all at once, allowing for higher image quality at real time, in only few milliseconds (Gennisson et al., 2013). Supersonic shear imaging has been used in the past years to assess the stiffness of several organs, with good reproducibility (Cosgrove et al., 2012) and specificity (Berg et al., 2012).

Recently, SWE has been used in musculoskeletal applications, especially following the determination of excellent correlation between shear modulus and muscle passive tension (Eby et al., 2013; Koo, Guo, Cohen, & Parker, 2013). The validation study conducted by Eby et al (2013) determined that the transducer orientation is crucial for reliable measures of shear modulus. Only a parallel orientation of the transducer in relation to the muscle fibers showed good correlation with the muscle passive tension. When the transducer was perpendicular, or at 45º, with the muscle fibers, there was poor correlation between the shear modulus and passive tension (Eby et al., 2013).

As a consequence of these validity and reliability studies, SWE, and in particularly SSI, started to be the chosen method of several investigations regarding muscle-tendon stiffness assessment, mainly: effects of stretching in muscle shear modulus (Freitas, Andrade, Antoine, Bruno, & Pedro, 2016; Freitas, Andrade, Larcoupaille, Mil-homens, & Nordez, 2015; Koo, Guo, Cohen, & Parker, 2014; Le Sant, Ates, Brasseur, & Nordez, 2015; Miyamoto, Hirata, & Kanehisa, 2015; Nakamura et al., 2014; Umegaki et al., 2015); determination of muscle shear modulus during muscle contraction (Ateş et al., 2015; Muraki et al., 2015; Raiteri, Hug, Cresswell, & Lichtwark, 2016; Yoshitake, Takai, Kanehisa, & Shinohara, 2014) assessment of tendon shear modulus (Cortes, Suydam, Silbernagel, Buchanan, & Elliott, 2015; Fu, Cui, He, & Sun, 2016; Rosskopf et al., 2016; Slane, Martin, DeWall, Thelen, & Lee, 2016); and even the stiffness of the shoulder joint capsule (Takenaga et al., 2015). Shear wave elastography has also been used to study a number of clinical conditions (Dirrichs et al., 2016; Lee et al., 2014; Leong, Hug, & Fu, 2016) with the purpose of characterizing the affected structure regarding its stiffness, and to establish cut-off values for distinguish between physiological or pathological conditions. This may be important not only for injury prevention, but also as a guide for the rehabilitation process.

6.2. Shear wave elastography in the assessment of peripheral nerves

There is little doubt that tendons, and especially muscles, are the focus of the majority of published studies using SWE. To date, there are still few studies that use SWE to assess peripheral nerves. Not due to its lack of relevance or interest, but because it is more difficult to measure nerves. A recent study used US to measure several nerves CSA and observed that the median nerve has an average CSA of 11 mm^2 measured in the carpal tunnel; the tibial nerve, at the popliteal fossa, has 33 mm^2 ; and the sciatic nerve has 59.5 mm^2, measured below the gluteal fold (Jang, Cho, Yang, Seok, & Kim, 2014). To better understand how nerves are thin, the tendon of the tibialis anterior muscle, close to its distal insertion, has 26.4 mm^2 (Morales-Orcajo, Becerro de Bengoa Vallejo, Losa Iglesias, & Bayod, 2016), which is similar to the tibial nerve; the patellar tendon has 90 mm^2 (Wiesinger, Rieder, Kösters, Müller, & Seynnes, 2016), which represents almost twice the sciatic nerve, and the tibialis anterior muscle has a CSA of 777 mm^2 (Maddocks et al., 2014), 13 times the sciatic CSA. Therefore, even the larger nerve is a relatively thin structure, which together with its depth (i.e. approximately 4-5 cm) makes it difficult to measure, especially in a longitudinal view.

Nevertheless, some studies have recently been published using SWE to analyze the peripheral nerves stiffness, mainly the median (Greening & Dilley, 2016), tibial (Dikici et al., 2016), and sciatic (Andrade et al., 2016) nerves. Kantarci et al (2014) used SSI to measure the stiffness of the median nerve in people with CTS, in a resting condition (Kantarci et al., 2014). They found that people with CTS had higher median nerve stiffness when compared to healthy controls (Kantarci et al., 2014). The stiffness of the median nerve was also measured by Greening & Dilley, (2016), in different postures of the ULTT, in healthy participants. These assessments were also performed in a resting condition, and showed a significant increase in the nerve stiffness as the limb was moved into positions that elongate the nerve bed (Greening & Dilley, 2016). These authors reached the same conclusion for the tibial nerve, during a SLR maneuver (Greening & Dilley, 2016). Recently, Dikici et al (2016) studied the tibial nerve stiffness of people with diabetic neuropathy, also in a resting condition (i.e. supine, with the foot relaxed in slight plantar flexion), and concluded that it was significantly increased comparing to healthy controls (Dikici et al., 2016).

The first study, to our knowledge, that used SWE to measure a peripheral nerve during a dynamic action was performed by Andrade et al. (2016). In this study, participants laid prone, while a dynamometer passively rotated the ankle into dorsiflexion. This motion caused a distal excursion of the sciatic nerve, and a corresponding increase in its stiffness (Andrade et al., 2016). This investigation proved that it is reliable to non-invasively assess the sciatic nerve stiffness, in healthy participants, during a dynamic action (Andrade et al., 2016).

Following this up to date, and brief review, where the basic concepts and terminology were detailed, we will present the studies of this thesis. Each study will be presented in separate, but all will share the same organization: an Introduction stating the problem, relevance and objectives of the study; a Methods section, where the materials, experimental procedures, and statistical analysis will be detailed; a section where the main Results will be presented; and a section with the Discussion of the results found, as well as the limitations of the investigation, and recommendations for future research.

CHAPTER III - Effects of Lower Body Quadrant Neural Mobilization in Healthy and Low Back Pain Populations: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Neural mobilization (NM) is widely used to assess and treat several neuromuscular disorders. However, information regarding the NM effects targeting the lower body quadrant is scarce. ***Objectives:*** To determine the effects of NM techniques targeting the lower body quadrant in healthy and low back pain (LBP) populations. ***Design:*** Systematic review with meta-analysis. ***Method:*** Randomized controlled trials were included if any form of NM was applied to the lower body quadrant. Pain, disability, and lower limb flexibility were the main outcomes. PEDro scale was used to assess methodological quality. ***Results:*** Forty-five studies were selected for full-text analysis, and ten were included in the meta-analysis, involving 502 participants. Overall, studies presented fair to good quality, with a mean PEDro score of 6.3 (from 4 to 8). Five studies used healthy participants, and five targeted people with LBP. A moderate effect size (g = 0.73, 95% CI: 0.48 - 0.98) was determined, favoring the use of NM to increase flexibility in healthy adults. Larger effect sizes were found for the effect of NM in pain reduction (g = 0.82, 95% CI 0.56-1.08) and disability improvement (g = 1.59, 95% CI: 1.14 - 2.03), in people with LBP. ***Conclusion:*** Evidence suggests that there are positive effects from the application of NM to the lower body quadrant. Specifically, NM shows moderate effects on flexibility in healthy participants, and large effects on pain and disability in people with LBP. Nevertheless, more studies with high methodological quality are necessary to support these conclusions.

Keywords: Neurodynamics; Peripheral nerves; Slump; Flexibility; Pain; Disability

INTRODUCTION

Neural mobilization (NM) techniques are widely used to evaluate, and improve, the mechanical and neurophysiological integrity of the peripheral nerves (Shacklock, 1995) in clinical populations (Butler, 2000). These techniques include combinations of joint movements that promote either neural tensioning (i.e. through displacement of the nerve endings in opposite directions) or sliding (i.e. through displacement of nerve endings in the same direction (Coppieters et al. 2009). Several studies have successfully used NM to improve flexibility, in both healthy (Herrington and Lee, 2006) and clinical populations (Coppieters et al. 2003), and also to induce different amounts of neural excursion (Coppieters et al. 2015). This is particularly relevant because it has been reported that nerve properties (e.g. cross-sectional area) are altered in certain peripheral neuropathies (Lee and Dauphinée, 2005), and in upper limb nerve entrapment syndromes (Hough et al. 2007; Kantarci et al. 2014). These changes in the nerve properties may be associated with a compromised nerve function (Li and Shi, 2007; Rickett et al. 2010). In addition, it has also been shown that people with peripheral neuropathy have a higher lower body quadrant mechanosensitivity (Boyd et al. 2010). Consequently, the NM techniques are used as treatment for different neuromuscular disorders. Studies performed in participants with cervicobrachial pain (Allison et al. 2002; Nee et al. 2012), lateral epicondylalgia (Vicenzino et al. 1996), and carpal tunnel syndrome (Pinar et al. 2005) have shown positive effects of NM interventions in pain relief. Some of these studies also found a positive effect in pain-free grip strength (Vicenzino et al. 1996; Pinar et al. 2005), and in self-reported activity limitations (Nee et al. 2012). The positive effects of NM reported in these studies are related to the upper body quadrant disorders (i.e. cervical spine, shoulder, elbow and wrist). Still, few studies have examined the NM effects on the lower body quadrant (i.e. trunk, thigh, leg and foot).

Low back pain (LBP) is a common lower body quadrant problem, and represents an important cause of disability with strong economic impact (Hoy et al. 2012; Global Burden of Disease Study 2013 Collaborators, 2015). Several interventions, such as exercise therapy (Hayden, 2005), massage (Furlan et al. 2009), or lumbar stabilization techniques (Haladay et al. 2013) are used to treat people with LBP, but with limited evidence regarding its effectiveness. In addition, NM has also been used to treat LBP

(Schäfer et al. 2011; Čolaković and Avdic, 2013), with the objective of reducing the patient's mechanosensitivity of the lower body quadrant (Coppieters et al. 2005).

Previous systematic reviews (Ellis and Hing, 2008; Su and Lim, 2015) examined the effects of NM interventions exclusively in clinical populations, and mostly in the upper body quadrant dysfunctions. Considering the recent NM studies published in both healthy and LBP populations, and the lack of meta-analytical data supporting the effects of NM, the purpose of this study was to systematically review appropriate randomized controlled trials (RCTs) that aimed to determine the effectiveness of NM techniques targeting the lower body quadrant. Specifically, we analyzed the effects of NM on flexibility in healthy adults, and the effects of NM on pain and disability in people with LBP.

METHODS

The protocol of this systematic review was registered on the International Prospective Register of Systematic Reviews (PROSPERO; CRD42015023602). This systematic review followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (Moher et al. 2009).

Search strategy and study selection

A comprehensive electronic search of scientific articles was conducted by one researcher (TN) on the following electronic databases: PubMed, PEDro, Web of Science, Scielo, and Cochrane Central Register of Controlled Trials. The following search terms were used (an example of a search strategy is shown in Appendix 1): neurodynamics, neural mobilization, neural tension, neural stretching, lower body quadrant, lower limb, low back pain, sciatica, flexibility, range of motion, physical therapy, neural stiffness, slump, straight leg raise test. This search was complemented by manually detecting references from bibliography of the included studies and previous reviews. A researcher (TN) identified the studies by their title and abstract, and manually removed the duplicate articles. When studies fulfilled the inclusion criteria, three researchers (TN, SF, and RO) read the entire manuscripts and gave their recommendation for inclusion.

Inclusion and exclusion criteria

Population

Studies using NM techniques in both healthy, and LBP participants, over 18 years of age were included. Low back pain was defined as the presence of pain and discomfort below the costal margin and above the gluteal folds with or without leg pain (Koes, 2006). Studies involving populations presenting other neuromuscular or rheumatic disorders, post-surgical conditions, and pregnancy were excluded.

Intervention

Eligible studies had to include any form of NM (i.e. sliding or tensioning) targeted to the lower body quadrant. Studies also had to compare NM against other forms of interventions (e.g. lumbar stabilization exercises, lumbar spine mobilization, static stretching, or standard treatment), or a control condition (no intervention or placebo). Due to the low number of studies that analyzes the effects of NM, a specific comparison intervention was not selected. Moreover, the objective was to assess the effects of the NM techniques, regardless of the interventions used as comparison, and not to conclude if NM is more effective than one determined intervention.

Outcomes

Eligible studies included at least one of the following outcomes: pain intensity (measured with a visual analogue scale or a numeric rating scale), disability (measured by the Oswestry Disability Index or the Roland and Morris Disability Questionnaire), or lower limb flexibility (measured by the straight leg raise test – SLR, or the active knee extension test – AKE).

Study characteristics

Studies had to meet the following inclusion criteria: a) written in English or Portuguese language; b) randomized controlled trials (RCTs); c) published between January 1995, and May 2015; and d) use any form of NM technique (i.e. sliders or tensioners) targeting the lower body quadrant. Studies involving animal or cadaveric investigations were excluded.

Quality Assessment

Methodological quality assessment (Table 1) of the selected studies was independently performed by two reviewers (TN, LG) using the PEDro scale (Verhagen et al. 1998). Initial disagreements were resolved by a consensus meeting between both reviewers. External validity was assessed using the first item of the scale. However, this criterion was not considered for the final PEDro score. Items 2-9 assess internal validity; items 10 and 11 refer to the study's statistical analysis (Maher et al. 2003). Depending on their PEDro score, studies were classified as excellent (PEDro score > 8), good (PEDro score between 6 and 8), fair (PEDro score between 4 and 5), and poor (PEDro score < 4) (Foley et al. 2003). The reliability between the two reviewers was determined using the Kappa statistics.

Data extraction

Data extraction was performed by one author (TN). The following information was extracted from each study: 1) bibliographic information (authors and year of publication); 2) objectives; 3) characteristics of the participants (age, sex, healthy/LBP participants, symptoms duration); 4) characteristics of NM interventions [technique type (i.e. sliders or tensioners), number of sessions, number of repetitions, and duration); 5) type of control condition (e.g. static stretching, manual therapy, exercise, standard treatments, placebo interventions, no intervention, and respective frequency and duration); 6) outcomes measured (e.g. pain, disability, lower limb flexibility). All outcomes variables were continuous. Effect sizes were determined using the following data: sample sizes, means, and standard deviations (SD), both at baseline and post-treatment, for all groups (i.e. treatment and control). In one study (Castellote-Caballero et al. 2013), there was no data on SDs, so the confidence intervals were extracted to calculate effect sizes. The studies of Webright et al. (1997) and Castellote-Caballero et al. (2014) used two control groups, one active (i.e. static stretching) and one passive (i.e. placebo intervention or no intervention). In this case the active control group was chosen for comparison.

Data synthesis

Considering that all studies shared basic methodological aspects (e.g. all were RCT), and that clinical studies used participants with similar characteristics (e.g. people with non-acute LBP), we considered appropriate to pool data for the meta-analysis. Consequently, separate meta-analyses were performed for each outcome of interest (pain, disability and flexibility). Meta-analyses were conducted using a fixed-effect model due to the number of included studies (Borenstein et al. 2011). Analyses were conducted using the Comprehensive Meta-Analysis Software version 2 (Borenstein et al. 2005). Effect sizes were determined by the standardized mean difference [(mean a − mean b / pooled change SD)] with Hedge's g correction for small samples (Hedges, 1981), and classified according to Cohen's guidelines (Cohen and Jacob, 1992) as small (0.20), medium (0.50), and large (0.80) effects. For each effect size, 95% confidence intervals (CI) were calculated. *Z*-values and corresponding p-values were considered as indicators of the significance of the pooled effects. For the one study (Sharma et al. 2015) with two intervention groups (*vs* one control group), a weighted mean combined effect was used (i.e. a composite variable that corresponds to the mean of intervention of group A *vs* control, and the mean of intervention of group B *vs* control. The variance of this composite is based on the variance of each effect size as well as the correlation between the two effects - Borenstein et al. 2011). This composite was calculated in Comprehensive Meta-Analysis Software.

To evaluate the amount of variation in the effects of included studies, statistical heterogeneity was inspected using: 1) the Cochran's Q statistic (Cochran, 1954), for which a significant p-value (<0.05) demonstrates that studies do not share a common effect size, and 2) I^2 statistic (Higgins et al. 2003) that assesses the proportion of observed dispersion that is due to real differences in the true effect sizes (rather than sampling error). The I^2 ranges from 0 to 100%, with values of 25%, 50% and 75% reflecting low, moderate and high statistical heterogeneity, respectively (Higgins et al. 2003).

RESULTS

Search results

Figure 2 presents the results for the studies selection process. A total of 4928 articles were screened by title and abstract. After duplicate removal, 45 studies were selected for full-text analysis. During analysis, 35 studies were excluded: 20 studies due to inappropriate intervention (i.e. did not use NM techniques, or did not measure its effects); 14 studies did not follow an appropriate design (i.e. RCT design); and one study was written in Korean. Ten eligible studies were therefore selected for qualitative and quantitative analysis.

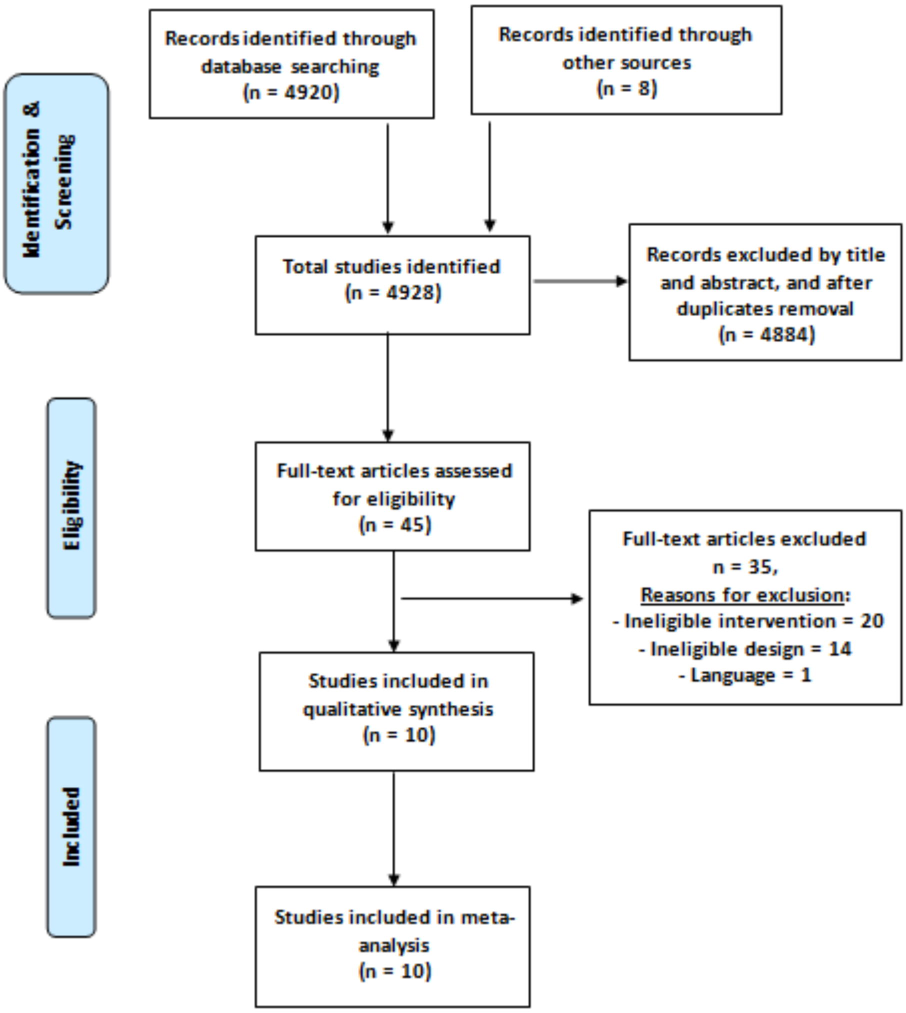

Figure 2. Flow of studies through the review

Methodological quality assessment

A very high inter-rater agreement was found for the PEDro scores (κ = 0.87, CI = 0.63 - 1.00, $p < 0.001$). Methodological quality scores ranged from 4 to 8, with a mean score of 6.3 points. The mean PEDro score for the five studies in healthy subjects and the five studies in people with LBP, was, respectively, 6.6 points and 6.0 points (Table 1). Three studies scored under 6 points (Dwornik et al. 2009; Machado and Bigolin, 2010; Čolaković and Avdic, 2013), and the remaining seven studies presented scores ranging from 6 to 8, which are considered to be of good quality. Items 2 (i.e. random allocation), 9 (i.e. intention-to-treat analysis), and 11 (i.e. point measures and measures of variability) were reported in all studies. However, blinding of the participants (item 5) and blinding of the therapists (item 6) were absent from all studies. Between-group comparisons (item 10) were performed in all studies, except for one study (Dwornik et al. 2009). All studies reported no differences in baseline characteristic (clinical and demographic) between groups with the exception of one study (Machado and Bigolin, 2010). Studies with scores lower than 7 also failed to conceal subjects' allocation.

Table 1. PEDro scores of the included studies

Study	Random allocation	Concealed allocation	Groups similar at baseline	Participant blinding	Therapist blinding	Assess or blinding	< 15% dropouts	Intention-to-treat analysis	Between-group difference reported	Point estimate and variability reported	Total (0 to 10)
Castellote-Caballero et al (2013)	Y	N	Y	N	N	Y	N	Y	Y	Y	**6**
Castellote-Caballero et al (2014)	Y	N	Y	N	N	Y	N	Y	Y	Y	**6**
Cleland et al (2006)	Y	Y	Y	N	N	Y	Y	Y	Y	Y	**8**
Colakovic and Avdic (2013)	Y	N	Y	N	N	N	N	Y	Y	Y	**5**
Dwornik et al (2009)	Y	N	Y	N	N	N	N	Y	N	Y	**4**
Machado and Bigolin (2010)	Y	N	N	N	N	N	Y	Y	Y	Y	**5**
Mendez-Sanchez et al (2010)	Y	Y	Y	N	N	Y	N	Y	Y	Y	**7**
Nagrale et al (2012)	Y	Y	Y	N	N	Y	Y	Y	Y	Y	**8**
Sharma et al (2015)	Y	Y	Y	N	N	Y	Y	Y	Y	Y	**8**
Webright et al (1997)	Y	N	Y	N	N	N	Y	Y	Y	Y	**6**

Y = Yes; N = No

Summary of qualitative analysis

Table 2. Characteristics of the included RCTs on healthy populations

Study	Participants Characteristics	NM Intervention	Comparison condition	Outcomes
Castellote-Caballero et al. (2013)	N = 28 Age (*yr*) = 20.8 (SD 1) Gender = 28 M	5 × 60 s repetitions of alternated head and lower limb movements, in a slump position; 3 sessions during one week	No intervention	LLF was measured pre and post-intervention by the passive SLR
Castellote-Caballero et al. (2014)	N = 120 Age (*yr*) = 33.4 (SD 7.4) Gender = 60 M, 60 F	1 session of 3 min. of a passive sciatic neural sliding technique in prone position	*Active control* – 5 reps x 30 s of passive hamstrings static stretching in SLR position; *Placebo control* – 3 min. of intrinsic foot joints passive mobilization	LLF was measured pre and post-intervention by the passive SLR
Mendez-Sanchez et al. (2010)	N = 8 Age (*yr*) = 21 (SD 3) Gender = 8 M	5 min. of static bilateral hamstrings stretching + sciatic slider NM, during 60 s, for each lower limb	5 min. of static bilateral hamstrings stretching	LLF was measured pre and post-intervention by the passive SLR
Sharma et al (2015)	N = 60 Age (*yr*) = 22 (SD 2.4) Gender = 33M, 27 F	*Group 1* - 30 s of static hamstrings stretching + 3 progressive sets (10, 15, and 20 reps) of neural sliding exercises, in slump position; *Group 2* - 30 s of static hamstrings stretching stretching + 3 progressive sets (10, 15, and 20 reps) of neural tension exercises, in slump position; 3 sessions during one week	30 s of static hamstrings stretching 3 sessions during one week	LLF was measured pre and post-intervention by the AKE test. The final knee extension angle was assessed with an inclinometer.
Webright et al (1997)	N = 40 Age (*yr*) = 21.3 (SD 3.6) Gender = 22 M, 18 F	30 reps. of AKE in slump position 2 x /day, for 6 weeks	*Active control* – 30 s of static hamstrings stretching, 2 x /day, for 6 weeks; *Passive control* – no intervention	LLF was measured pre and post-intervention, by videorecording the knee ROM during AKE

AKE (Active Knee Extension); F (Female); LLF (Lower Limb Flexibility); M (Male); NM (Neural Mobilization); ROM (Range of Motion); SD (Standard Deviation); SLR (Straight Leg Raise); *Yr* (Years)

Table 3. Characteristics of the included RCTs on people with LBP

Study	Participants	NM Intervention	Control Intervention	Outcomes
Cleland et al. (2006)	N=30, NRLBP symptoms for 18.5 (NM group) and 14.5 (Control group) weeks Age (*yr*) = 38.7 (SD 11.6) Gender = 9 M, 21 F	Lumbar vertebrae mobilization and exercise + 5 × 30 s of slump static stretching, performed 2×/week, for 3 weeks	Lumbar vertebrae mobilization and exercise	Pain (NRS) and disability (ODI) were measured before and after the 3 weeks intervention period
Colakovic and Avdic (2013)	N=60, with radicular LBP Age (*yr*) = 43.1 (SD 6.4) Gender = 30 M, 30 F	3 series of 10 reps. of oscillatory movements combining knee extension, hip flexion, and ankle dorsiflexion, Intervention was applied 3x/week, during 4 weeks.	Active ROM exercises for back and lower limbs, plus lumbar stabilization exercises	Pain intensity was measured with a VAS, which was later converted to a NRS. Measurements were made before and after the intervention
Dwornik et al.(2009)	N = 87, chronic LBP with neurogenic functional pain referred to the lower extremities Age (*yr*) = 43 (SD 10) Gender = 34 M, 53 F	10 sessions of NM techniques, applied to the trunks of the femoral, sciatic and tibial nerves, over a 2 week period	10 sessions of standard physiotherapeutic treatment	Pain intensity was measured with a VAS, which was later converted to a NRS. Measurements were made before and after the intervention
Machado and Bigolin (2010)	N = 9, LBP symptoms for over a 3 months period Age (*yr*) = 44.2 (SD 8.5) Gender = 2 M, 7 F	SLR maneuvers, and an additional 3 neural tensioning exercises, during 30 min., 2×/week, for a total of 20 sessions	Active and passive stretching of all trunk and lower limb muscle groups	Pain intensity was measured with a VAS, which was later converted to a NRS; RMDQ was used to assess disability. Measurements were made before and after the intervention
Nagrale et al (2012)	N = 60, NRLBP symptoms with 15 weeks of duration Age (*yr*) range = 18 to 60 Gender = 21 M, 39 F	Lumbar spine mobilization and stabilization exercises + + 5 × 30 s of slump stretching performed 2×/week, for 3 weeks	Lumbar spine mobilization and stabilization exercises	Pain (NRS) and disability (ODI) were measured before and after the 3 weeks intervention period, and after a 3 week follow-up period.

F (Female); LBP (Low Back Pain); M (Male); NM (Neural Mobilization); NRLBP (Non Radicular Low Back Pain); NRS (Numeric Rating Scale); ODI (Oswestry Disability Index); RMDQ (Roland and Morris Disability Questionnaire); SD (Standard Deviation); VAS (Visual Analogue Scale); *Yr* (Years)

Characteristics of the included studies

The included studies involved a total number of 502 participants (male: n=49.2%; female: n=50.8%; mean age of 32.7, SD = 10.2 years), in which 256 (51.0 %) were healthy participants (Table 2) and 246 (49.0%) were LBP participants (Table 3). Five studies measured the effects of NM techniques in healthy participants (Webright et al. 1997; Méndez-Sánchez et al. 2010; Castellote-Caballero et al. 2013, 2014; Sharma et al. 2015) and five studies measured the effects of NM techniques in people with LBP (Cleland et al. 2006; Dwornik et al. 2009; Machado and Bigolin 2010; Nagrale et al. 2012; Čolaković and Avdic, 2013). Flexibility of the lower limbs was measured in five studies: three studies using the SLR test (Méndez-Sánchez et al. 2010; Castellote-Caballero et al. 2013, 2014), and two studies using the AKE test (Webright et al. 1997; Sharma et al. 2015). In relation to LBP studies, five assessed pain using a numeric scale (Cleland et al. 2006; Dwornik et al. 2009; Machado and Bigolin 2010; Nagrale et al. 2012; Čolaković and Avdic, 2013), three studies measured disability [(two used the Oswestry Disability Index (Cleland et al. 2006; Nagrale et al. 2012), and one used the Roland and Morris Disability Questionnaire (Machado and Bigolin, 2010)].

Neural mobilization interventions

Neural mobilization techniques performed in the slump test position were the most common. Two studies (Webright et al. 1997; Castellote-Caballero et al. 2013) performed NM sliding techniques, and other two (Cleland et al. 2006; Nagrale et al. 2012) used NM tension techniques; Sharma et al. (2015) used both NM tension and sliding techniques. The studies of Méndez-Sánchez et al. (2010), Castellote-Caballero et al. (2014), and Colakovic & Avdic (2013) used a combination of passive movements in the lower limb to promote neural sliding. Two studies (Dwornik et al. 2009; Machado and Bigolin, 2010) did not specify the type of NM technique used. The number of NM sessions ranged from 1 (Castellote-Caballero et al. (2014); Méndez-Sánchez et al. 2010), to 90 (Webright et al. 1997). In the studies that performed only one session, the NM technique lasted from 60 s (Méndez-Sánchez et al. 2010), to 180 s (Castellote-Caballero et al. 2014). In the remaining studies, the duration of NM ranged from 150 s (Cleland et al. 2006; Nagrale et al. 2012), to 300 s (Castellote-Caballero et al. 2013). The most frequent number of repetitions, per session, was five (ranging from 1 to 45).

Effects of Neural Mobilization on Flexibility

The results of NM techniques effects on flexibility are presented in the Figure 3. Five studies showed a significant medium effect size (k=5; g=0.73; 95% CI = 0.49-0.98; z=5.71 p<0.001) favoring the use of NM to increase flexibility. The largest effect size (g = 1.38) was found in the trial conducted by Castellote-Caballero et al. (2013) that compared three sessions of active neural siding, in a slump position, with no intervention. Participants who performed NM had a significant increase in flexibility (i.e. 16%). The remaining four studies compared NM to static stretching. We performed an additional meta-analysis targeting these four studies, without the Castellote-Caballero et al. (2013) paper, to determine the influence of this study (i.e. which did not use static stretching for comparison to NM) in the global effect size. The resulted combined effect size (g = 0.66; 95% CI = 0.39 – 0.62) was similar to that obtained in the initial analysis, with all the five studies (g = 0.73). The smallest effect size (g = 0.14) was found in the study by Webright et al. (1997), in which interventions based on NM were just as effective in increasing hamstrings extensibility as static stretching. There was low statistical heterogeneity between trials (Q = 6.22, p = 0.18; I^2 = 35%).

Treatment effects on flexibility

Study name	Outcome	Statistics for each study			Sample size	
		Hedges's g	Lower limit	Upper limit	Treatment	Control
Castellote, 2013	Flexibility	1,381	0,576	2,186	14	14
Castellote, 2014	Flexibility	0,642	0,257	1,028	40	80
Mendez-Sanchez et al, 2010	Flexibility	0,749	-0,510	2,009	4	4
Sharma, 2015	Flexibility	0,905	0,453	1,357	40	40
Webrigth et al, 1997	Flexibility	0,135	-0,546	0,816	11	29
		0,730	0,480	0,981		

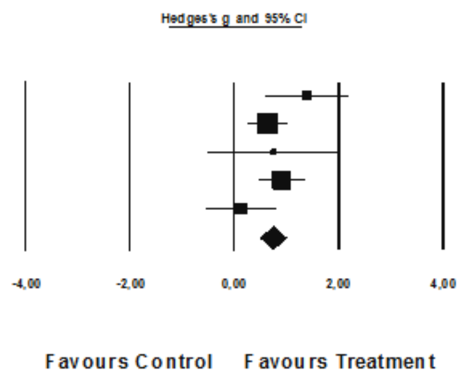

Figure 3. Forest plot of NM effects on lower limb flexibility

Effects of Neural Mobilization on Pain

The effects of the NM maneuvers on pain were reported in five studies (Figure 4). Sample sizes ranged from 9 (Machado and Bigolin, 2010), to 87 participants (Dwornik et al. 2009). Overall, interventions yielded large effect sizes (g = 0.82; 95% CI = 0.56-1.08; z = 6.25, p<0.001) on pain levels in patients with LBP. The largest effect sizes (g = 1.31 and g = 1.23) were observed in the studies of Cleland et al. (2006) and Nagrale et al. (2012), respectively.

These studies concluded that adding neural stretching in a slump position to a lumbar spine mobilization and exercise program was more effective in decreasing pain than just performing lumbar spine mobilization and exercise. The trials by Dwornik et al. (2009), and Čolaković & Avdic (2013) presented medium effect sizes (g = 0.64 and g = 0.58, respectively) favoring the use of NM in pain reduction, compared to other interventions (i.e. standard physiotherapeutic treatment, and a combination of exercises for back and lower limbs and plus lumbar stabilization, respectively). The study of Machado and Bigolin (2010) revealed a small effect size (g = 0.43) also favoring the use of NM, compared to muscle stretching. It was observed a low statistical heterogeneity between trials (Q = 5.64, p = 0.23; I^2 = 29%).

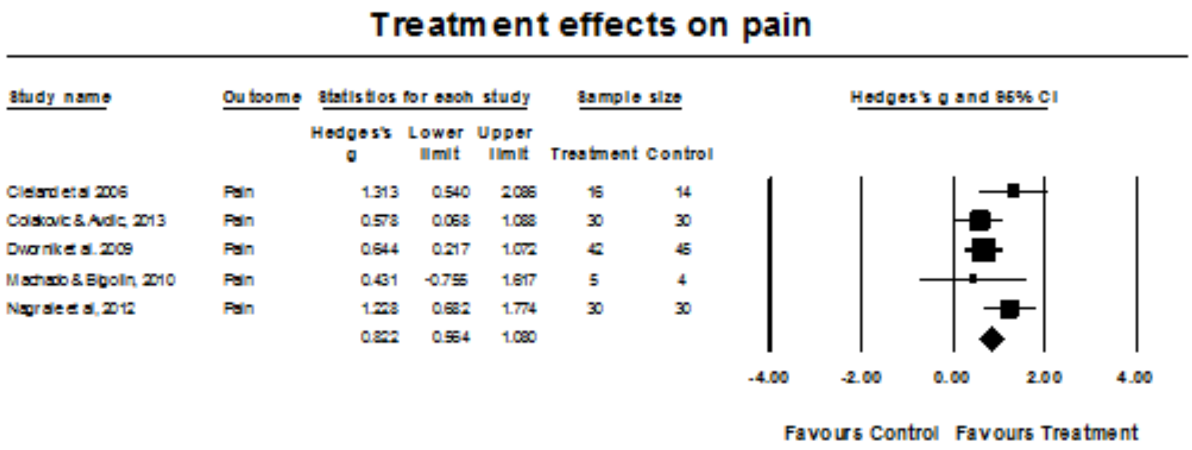

Figure 4. Forest plot of NM effects on Pain

Effects of Neural Mobilization on Disability

The effects of the NM techniques on disability are reported in Figure 5. Only three studies presented results for the effects of NM on disability. The overall effect size was large (g = 1.59, 95% CI = 1.14–2.03; z = 7.01, p<0.001), favoring the use of NM to decrease disability in people with LBP. The Cleland et al. (2006) study showed the largest effect size (g = 1.82), and it was followed by the RCT conducted by Nagrale et al. (2012) (g = 1.62). In both studies, NM consisted of six treatment sessions, which showed better results when added to a lumbar spine mobilization and exercise program, than just performing lumbar spine mobilization and exercise. The smallest effect size, though large (g = 0.92), was found in the RCT conducted by Machado and Bigolin (2010), which also presented the smallest sample size (N = 9). There was no evidence of statistical heterogeneity between trials (Q = 1.41, p = 0.49, I^2 = 0.00).

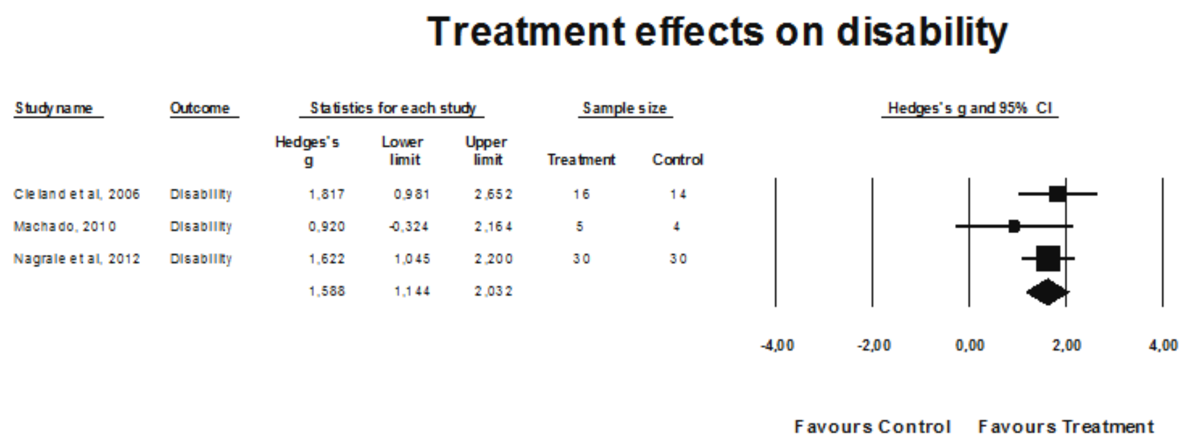

Figure 5. Forest plot of NM effects on Disability

DISCUSSION

The present study systematically reviewed and performed a meta-analysis regarding the effectiveness of NM techniques targeting the lower body quadrant, in both healthy and LBP participants. Two main findings were observed: i) Evidence from the pooled effect sizes suggests that NM interventions, either used alone or in combination with other treatments, successfully decreased pain levels and disability in people with LBP, and increased flexibility in healthy adults; and ii) a large variability was observed regarding the parameters of the NM interventions, such as the type of technique applied, number of sessions, and duration of the intervention.

This systematic review shows that NM techniques have a medium effect size (g = 0.73) on the increase of flexibility in healthy populations. Additionally, the combined effect size found (g = 0.66) when we analyzed only the studies that used static stretching as a comparison for NM, still represents an indication for larger improvements in flexibility. This finding was already observed (Ellis and Hing, 2008), and suggests that the peripheral nerves may influence flexibility. Recently, one study (Andrade et al. 2015a) reported that the resistance to stretch (i.e. passive torque), during the passive knee extension test, was influenced by cervical and thoracic spine flexion. In addition, another study (Andrade et al. 2015b) concluded that ankle dorsiflexion maximal range of motion (ROM) was lower (i.e. by 17.7 °) in a hip flexed position, whereas no alterations occurred in ankle passive torque or medial gastrocnemius passive tension. Since there is no muscle-tendon complex crossing both ankle and hip joints, it was suggested that the decrease of ROM was due to an increase of the sciatic nerve tension. However, to date no studies have directly examined the influence of neural tension on joints' flexibility. This may help to explain the effectiveness of NM techniques to improve flexibility that was observed in the present review.

The results from the meta-analysis also shows a large beneficial effect of using NM techniques to reduce pain (g = 0.82) and disability (g = 1.59) in people with LBP. Keeping in mind that these are global effect sizes determined from only five studies (i.e. and only three for disability), the effect sizes calculated for each individual study also supports the positive effects from the application of NM. The benefits from the use of NM were seen either in combination with other treatments (e.g. exercise), or by using NM alone, and were always superior the control interventions. These results are in accordance with the review of Ellis and Hing (2008) that examined the efficacy of NM techniques, and reported that eight out of the eleven studies included showed positive effects in pain and disability. Our results are also similar to the ones reported in a recent meta-analysis (Sun and Lim, 2015). The study of Su and Lim (2015) reports moderate (g = 0.77) and large (g = 1.06) effects favoring the use of NM for decreasing pain, and disability, respectively, when compared to minimal intervention (e.g. when the control group received the same intervention as the experimental group, with the exception for the NM interventions).

The physiological mechanisms underlying such effects on these variables are still unexplored. Studies showed that functionally intact C-fibers, in locally inflamed nerves, develop mechanosensitivity to pressure and stretch, (Dilley and Bove, 2008). Consequently, interventions aimed to reduce intraneural pressure may have positive effects in inflamed nerves. One cadaveric study has confirmed that NM applied to the tibial nerve (i.e. using passive ankle mobilization) produced intraneural fluid dispersion, caused by an intermittent change in intraneural pressure (Brown et al. 2011). Similarly, another study in human cadavers has concluded that repeated NM (i.e. straight leg raise maneuvers) increased longitudinal fluid dispersion in the fourth lumbar nerve root (Gilbert et al. 2015). This "pumping" effect is thought to facilitate the axonal transport, and minimize the deposition of sensitizing chemicals, which may result in pain relief and improved function (Brown et al. 2011). However, no studies have confirmed *in vivo* these hypotheses. Recently, Andrade et al. (2015c) used shear wave velocity to infer about the sciatic nerve stiffness. There was a tendency for the nerve´s stiffness to reduce throughout five cycles of plantar flexion-dorsiflexion, with the knee in full extension. In addition, there was a presence of hysteresis (Andrade et al. 2015c). Consequently, it seems that neural mechanical properties can be altered by repetitive tensile stresses. Considering that some mechanical peripheral nerve dysfunctions (e.g. lumbar radiculopathies) are associated to a compromised neural function

(Li and Shi, 2007; Rickett et al. 2010), the use of NM may have an effect on the biomechanical properties of the nerve, which may lead to the improvements in pain and disability found in this review. This should be examined *in vivo*.

The second finding of this review is related to the high variability of the NM parameters in the studies included, mainly regarding the type of NM technique used, the NM load applied (i.e. intensity and duration), the number of repetitions, and the number of sessions used in both healthy and LBP populations. This variability, together with the fact that some studies did not report the NM parameters (e.g. type of NM or number of repetitions/sessions performed), makes it difficult to draw conclusions regarding the appropriate NM protocol. In addition, two different tests were used to assess lower limb flexibility: the SLR (i.e. targeting hip flexion with the knee fully extended) and the AKE (i.e. targeting knee extension with the hip flexed at 90°). Both tests are highly reliable (ICC of 0.87-0.94 and 0.93–0.97, respectively for AKE and SLR) and frequently used to assess lower limb flexibility (Gajdosik et al. 1993; Neto et al. 2014). However, they present different characteristics: the tests target different joints (i.e. hip vs. knee); the motion varies between active (AKE) and passive (SLR); they promote different sciatic excursion values (Coppieters et al. 2015); and the mechanical effects (i.e. stiffness reduction) on hamstrings muscles vary between passive SLR and knee extension exercises (Le Sant et al. 2015, Miyamoto et al. 2015). Therefore, these methodological differences should be considered when comparing flexibility values obtained from these two tests.

This review included a limited number of trials (between 3 and 5 for each meta-analysis) that used NM to target the lower body quadrant. This limits the conclusions that can be derived from the analysis, as non-significant effects may be due to low statistical power, and combined effects influenced by trials with larger samples. Considering this limitation, it is important to analyze not only the overall effect size, but also the effect size determined for each study. The individual effect sizes show us that in most cases, with the exception of Webright et al. (1997), NM was consistently more effective than the control intervention used. Moreover, included studies presented several methodological limitations. The most frequent limitations were related to non-blinding characteristic of studies, and also participants' allocation concealment. In addition, one study (Machado and Bigolin, 2010) showed baseline differences between groups (i.e. in pain scores), which may represent a source of bias if between-group comparisons are performed. However, for this meta-analysis we used within-group, and not between-group, differences in pain scores.

Future investigations should address the aforementioned limitations found in the studies included in this review, in order to improve their methodological quality. In addition, the methodology used for the NM interventions should be detailed (e.g., type of technique, number of sessions, and load) to standardize the clinical intervention and therefore its outcomes. In forthcoming studies, it would be relevant to compare, not only different NM techniques (e.g. sliders and tensioners), but also different protocols (i.e. different number of repetitions, sessions, and durations) in order to determine its effectiveness. It would also be relevant to include follow-up assessments, which could provide relevant information regarding the long term benefits of NM interventions.

We also encourage further research underlying the physiological effects of these techniques beyond its clinical effects. For example, it would be relevant to analyze *in vivo* the effects of NM techniques on the mechanical properties of the nerves (Andrade et al. 2015c). This would represent valuable information for the rehabilitation of several peripheral neuropathies and neuromuscular disorders.

CONCLUSIONS

The results from this systematic review and meta-analysis suggest that NM techniques have a positive effect on flexibility of healthy subjects, and also show benefits on pain relief and functional improvements in LBP populations. This systematic review with meta-analysis provides evidence, through the analysis of RCTs, on the effects of NM techniques applied to the lower body quadrant. However, a higher number of good quality RCTs, with robust comparison groups, and longer follow-ups, are needed to provide solid conclusions regarding the effectiveness of NM interventions.

Author’s contributions

All authors had a decisive and important role in this study. The research conception and study design were performed by TN, SF, MM, RA, and RO; Data collection was performed by TN, SF and RO; Data analysis was performed by TN, LG and MM; all authors contributed to the drafting of the article and revised it for important intellectual content; all authors read and approved the final version of the manuscript.

Conflicts of interest

None

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CHAPTER IV - Immediate effects of neural tension in a slump position in the sciatic nerve stiffness

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Status: Submitted, under review

ABSTRACT

Background: The slump test position is used to assess and improve the mechanosensitivity of peripheral nerves, for instance in people with chronic low back pain. It is also used as a technique for flexibility training in healthy individuals. However there is no evidence regarding the mechanical effects of this technique in the nerve properties. **Objectives:** To examine the immediate effects of neural tension in a sustained Slump position in the sciatic shear wave velocity (SWV, i.e. an index of stiffness), using an ultrasound-based shear wave elastography technique. **Design:** A cross-sectional study was conducted to assess the sciatic SWV and the ankle torque-angle. **Methods:** Fourteen healthy participants were assessed during passive ankle rotations (2°/s) before and immediately after the slump intervention (3 min) applied unilaterally to one lower limb, while the contralateral limb served as control. Muscle activation was also assessed using surface electromyography. **Results:** The slump intervention did not change the sciatic SWV (P = 0.78), nor the dorsiflexion passive torque (P = 0.14), throughout the ankle dorsiflexion motion. Ankle dorsiflexion increased the sciatic SWV from 50% of maximal range of motion (P = 0.04). Substantial reliability values were observed for the SWV assessment (ICC = 0.74-0.95). **Conclusions:** The sciatic nerve stiffness of healthy participants was not changed immediately after a neural tension intervention in a slump position. This suggests that the effects of nerve tensioning maneuvers (e.g. flexibility improvements) are not solely explained by changes of the nerve mechanical properties. These results ought to be confirmed in clinical populations.

KEYWORDS: Shear wave velocity; Elastography; Neurodynamics; Neural tension

INTRODUCTION

The slump test is used to determine the relationship between the patient's symptoms and restriction of movement of the pain-sensitive structures (Maitland 1979). Even if the peripheral nervous system is tested as a closed-chain continuum, the slump test is often used to examine the lower body quadrant mechanosensitivity of clinical patients (e.g. chronic low back pain population) (Urban and MacNeil 2015). It is also used as a rehabilitation technique with the purpose of restoring full pain-free range of motion (ROM) by a reduction in mechanosensitivity. It is suggested that neurodynamics techniques, such as the slump position, improve the mechanical properties of nerves and their relationship with mechanical interfaces (Butler 2000). However, this is yet to be confirmed. Briefly, the slump test involves the progressive addition of neural load: 1) thoracic and lumbar spine flexion; 2) cervical flexion; 3) knee extension; 4) ankle dorsiflexion. Previous studies have used the slump position to induce tensile loads to the nerves, mainly the sciatic nerve, either in clinical (Cleland et al. 2006; Nagrale et al. 2012), or healthy (Sharma et al. 2016) populations. It is hypothesized that the clinical benefits (i.e. pain relief and disability improvement) obtained from sustained slump test positions (e.g. 5 repetitions of 30 seconds) (Cleland et al. 2006) may be related to a decrease in the nerve stiffness (Cowell and Phillips 2002), but without any experimental direct evidence of such changes

Previous *ex vivo* experiments have demonstrated that nerves have viscoelastic responses (Wall et al. 1991) when submitted to limb motions that apply tensile longitudinal forces, such as the slump test (Driscoll et al. 2002; Ellis et al. 2012; Phillips et al. 2004). However, it is still unknown what are the effects of sustained tensile loads in the stiffness of human peripheral nerves. Recently, it was reported an asymmetry in the stiffness of medial nerves between the affected and unaffected limbs, in people with carpal tunnel syndrome (Kantarci et al. 2014). Consequently, it should be relevant to determine if neurodynamics interventions based in a slump position have an effect on the neural stiffness.

In the recent years, several studies have used ultrasound in B-mode to measure nerve excursion, in both healthy (Ellis et al. 2012; Ridehalgh et al. 2012; Ridehalgh et al. 2014) and clinical populations (Boyd et al. 2012; Ridehalgh et al. 2015), but this measurement does not provide a direct estimation of changes in neural stiffness. However, shear wave elastography is a method that allows to estimate the stiffness of soft tissues, including peripheral nerves (Andrade et al. 2016). This technique measures the shear wave velocity (SWV, i.e. an index of stiffness) within the soft tissues after a focused ultrasound push beam (Bercoff et al. 2004). Andrade et al. (2016) observed a sciatic nerve SWV increase during the passive ankle dorsiflexion movement when the knee was fully extended (i.e. a maneuver that is thought to strain the nerve). Additionally, it was observed a tendency for a decrease in SWV after five slow plantarflexion-dorsiflexion cycles. Although, it is unknown if sustained loading to the sciatic nerve, as performed in a clinical setting, would greatly decrease its intrinsic stiffness. Consequently, the purpose of this study was to determine, *in vivo*, the acute effects of neural tension in a slump position in the sciatic SWV using shear wave elastography. We hypothesized that the slump intervention would induce an acute decrease of the sciatic nerve SWV of healthy participants.

MATERIALS AND METHODS

Participants

Nineteen healthy volunteers were invited to participate in this study. Participants reported no neuromuscular disorders to the lower limbs or lower back, and signed the informed consent accordingly to the Declaration of Helsinki. This study was approved by the local Ethics Council (CEFMH Approval number: 3/2015).

Equipment

Dynamometry

An isokinetic dynamometer (Biodex system 3 research, Shirley, NY, USA) was used to passively dorsiflex the ankle joint (2°/s). Ankle angle and torque were sampled at 1000 Hz. Participants laid prone with the lateral malleolus aligned to the dynamometer axis (Fig. 6-A). The neutral position of the ankle (0°) was defined by the perpendicular position between the foot and leg, and determined by using an inclinometer.

Shear wave elastography

An ultrasound scanner (Aixplorer, version 10.0; Supersonic Imagine, Aix-en-Provence, France) was used to assess (1Hz) the sciatic SWV with a linear transducer array (SL 10-2 MHz, Super Linear, Vermon, Tours, France) in the muscular-skeletal preset (penetrate mode, smoothing level 9/9, and the persistence off). The maximal SWV scale value was set as 17.0 m/s. The sciatic nerve was first identified transversely (Fig. 6-B) by scanning the posterior thigh in B-mode, approximately 10 cm below the gluteal fold (Fig. 6-A), which was described as the best region for the sciatic nerve ultrasonographic assessments (Bruhn et al. 2008). Then, the probe was orientated longitudinally until both superficial and deep epineurium could be observed (Fig. 6-C). The probe location was marked in the skin with a waterproof marker, so repeated measures could be performed always in the same location (Fig. 6-A). Clip videos with both B-mode and shear wave elastography modes displayed were recorded during measurements.

Electromyography

Surface electromyography (EMG) was used to record muscle activation, to ensure a passive nature to the motion. A telemetric system (Plux, Lisbon, Portugal) was used, and surface electrodes (Ambu R BlueSensor N, Copenhagen, Denmark) were placed in the semitendinosus (ST), medial gastrocnemius (MG), and tibialis anterior (TA) mid-belly of both lower limbs, through guidance of ultrasound (B-mode). Signals were sampled at 1kHz rate, amplified (x 1000) and digitized (8 - 500 Hz bandwidth) before analysis. Resting EMG activity was deducted from the EMG values collected during the ankle dorsiflexion passive motion (Gajdosik 2006). EMG values were later normalized to the maximal isometric voluntary contraction (MIVC).

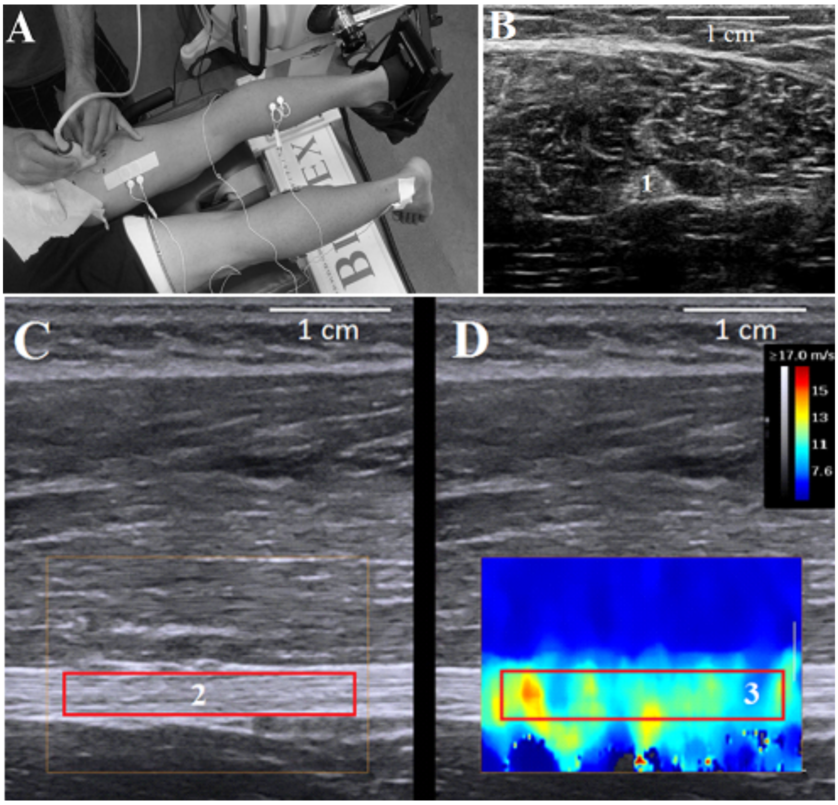

Figure 6. (A) Testing setup. B-mode sonograms of the sciatic nerve in (B) cross-sectional and (C) longitudinal views. The (D) elastogram window was defined over the nerve section, and the largest area within the epineurium was considered as region of interest

Legend: 1, Sciatic nerve cross-sectional area; 2, Sciatic nerve longitudinal view; 3, Sciatic nerve elastogram region of interest

Procedures

Participants visited the laboratory in one single session. Before testing, the experimental lower limb (i.e. the limb subjected to the slump intervention) and the control (i.e. contralateral) lower limb were randomly defined. Pre and post tests were performed with the participants laid prone in the dynamometer and the pelvis firmly strapped. The participants' maximal passive ankle dorsiflexion range of motion (ROM) was determined by using a hand-held stop button. The ankle movement was performed at 2°/s, and the participants were instructed to stop the movement when they reached the point of stretching discomfort. Approximately 3 min after the ROM determination, four plantarflexion-dorsiflexion cycles, starting from 40° of plantarflexion to the maximal dorsiflexion angle, were performed at 5°/s for conditioning purposes (Nordez et al. 2008). Thereafter, the SWV of the sciatic nerve and the ankle torque-angle were assessed in two maximal dorsiflexion ROM repetitions (2°/s). Between the two repetitions (1 min rest), the probe was removed from the site of measurement, for reliability purposes. After a 2 min rest period, the slump test sequence was performed to the experimental limb (Fig. 7). Briefly, participants were seated with their hands behind the back, and were asked to flex their lumbar and thoracic spine into a slump position. Afterwards, cervical spine flexion was added, and passively maintained in this position by an examiner. While the control limb stayed relaxed, the knee was passively extended by a second examiner, while the ankle was maximally dorsiflexed, until the point of stretching discomfort. This position was statically maintained during 3 min (Fig. 7). Immediately after the slump protocol, participants were re-positioned in prone position for the post testing. The post measurements were always performed first in the experimental limb, in order to rapidly assess the effects of the slump intervention. Finally, 3 MIVC repetitions for the knee flexors, plantar and dorsiflexors (1 min rest between repetitions) were performed for EMG normalization purposes.

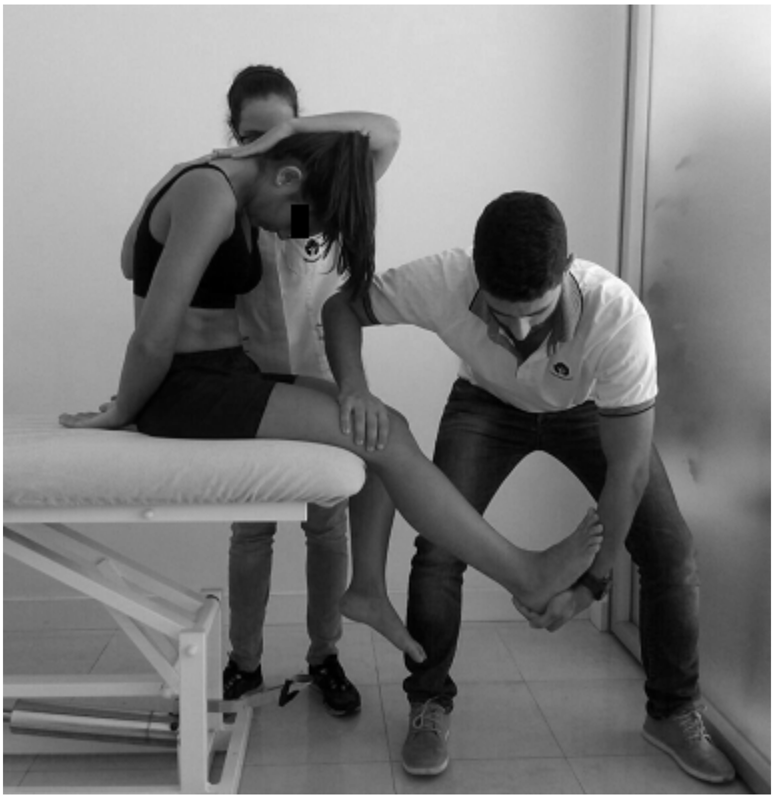

Figure 7. Slump test position

Data processing

All data acquisition was synchronized by using an external trigger, saved in a personal computer, and processed using customized MatLab routines (The Mathworks, Natick, USA). Briefly, in the sonograms clips, the sciatic region of interest was determined by selecting the largest area within the epineurium in the elastogram window (Fig. 6-D). This procedure was repeated for each frame (i.e. every second), to ensure that the region of interest would not be affected by the nerve motion during the maneuvers. When selecting the region of interest, careful was taken to avoid regions of saturation (i.e. values higher than the ones supported by the ultrasound device), since they are considered as artifacts. SWV values were calculated by converting the color pixels (in accordance with the scale) and averaged for statistical analysis. The sonograms clips with incomplete elastogram (i.e. elastograms in which the nerve region showed a partial absence of shear wave signal) were excluded from analysis.

The SWV was used instead of shear wave modulus, since the shear wave modulus is estimated by imaging the shear wave propagation in an infinite environment, or a source-free region (Bercoff et al. 2004), which may not be the case for the study of thin structures such as nerves (Andrade et al. 2016; Brum et al. 2014; Helfenstein-Didier et al. 2016).

As the ankle maximal ROM was different between the participants, the ankle angles were normalized to the maximal ROM. Ankle range until 80% of maximal ROM was considered for analysis. This ROM cut-off was also used in a previous study (Andrade et al. 2016), since the elastogram in some participants reaches the maximal value of the scale (i.e. 17 m/s), and considerable artifacts occur above this ankle ROM.

Statistical Analysis

The intraclass coefficient correlation ($ICC_{2,1}$) was determined to assess the intra-rater reliability of the shear wave velocity measurements. In addition, the standard error of measurement (SEM), the minimal detectable difference (MDD), and the coefficient of variation (CV) were determined. The SEM was calculated as follows: $SEM = \sqrt{MS_E}$, where MS_E represents the square root of the error mean square, obtained from the 2-way random effects analysis of variance. The MDD was determined by the formula $MDD = SEM \times 1.96 \times \sqrt{2}$, and the CV was calculated by dividing the standard deviation over the mean (Weir 2005). The reliability parameters were determined for every 10% interval of the ankle ROM.
The normality of the data was confirmed using the Shapiro-Wilk test. A 3-way repeated measures ANOVA [limb (control, experimental) × angle (0, 10, 20, 30, 40, 50, 60, 70, and 80 % of maximal ROM) × condition (pre, post)] was calculated to determine the effects of neural tension in the shear wave velocity of the sciatic nerve and in the ankle passive torque. The Bonferroni correction method was used for post-hoc analysis. Statistical significance was set at 0.05.

RESULTS

During data collection, 5 participants (3 male, 2 female; 30.4 ± 10.1 years; 75.6 ± 14.3 kg; 1.75 ± 0.1 m) were excluded due to an incomplete shear wave elastogram. Consequently, the data analysis was performed in 14 participants (11 male, 3 female; 28.4 ± 6.7 years; 69.6 ± 8.7 kg; 1.74 ± 0.08 m).

During all the tests, a 1.5% ± 1.1%, 2.0% ± 0.9%, and 2.8% ± 1.3% of muscle activation were observed for the semitendinosus, medial gastrocnemius, and tibialis anterior muscles, respectively.

The intra-rater reliability outcomes for sciatic nerve shear wave velocity assessment are presented in Table 4. Overall, substantial reliability was found for 0 to 70% ankle ROM percentiles, and moderate reliability was observed for the 80% ankle ROM percentile. The lowest ICC found was 0.74, and the highest SEM, MDD, and CV was 1.15 m/s, 3.19 m/s, and 8.66 %, respectively.

Table 4. Intra-rater reliability values of the sciatic nerve shear wave velocity, for every 10% interval of the total ankle range of motion.

% of Ankle ROM	ICC (95% CI)	SEM (m/s)	CV (%)	MDD (m/s)
0	0.93 [0.79 - 0.98]	0.46	4.31	1.27
10	0.93 [0.81 - 0.98]	0.42	4.78	1.18
20	0.88 [0.67 - 0.96]	0.53	5.42	1.48
30	0.89 [0.69 - 0.96]	0.51	4.97	1.43
40	0.95 [0.84 - 0.98]	0.35	3.38	0.98
50	0.89 [0.70 - 0.96]	0.54	5.46	1.51
60	0.88 [0.68 - 0.96]	0.57	5.75	1.58
70	0.83 [0.54 - 0.94]	0.80	6.72	2.22
80	0.74 [0.38 - 0.91]	1.15	8.66	3.19

ICC - Intraclass correlation coefficient; SEM - Standard error of measurement; MDD - Minimal detectable difference; CV - Coefficient of variation

In respect to the sciatic shear wave velocity (Fig. 8 -A), no significant interactions were found between the variables limb, condition, and ankle angle. Also, no significant main effects were found for the limb ($F_{1,13} = 0.648$, p = 0.435) or condition ($F_{1,13} = 0.082$, p = 0.779) variables. However, a significant main effect was found for the angle variable ($F_{8,104} = 47.604$, p < 0.001). Post hoc analysis revealed an increased SWV at 50% to 80% of ankle ROM compared to the 0% of ankle ROM in both the experimental (p = 0.04) and control (p = 0.01) limbs, and in both the pre (p = 0.01) and post (p = 0.02) intervention. Similarly, no significant interactions, and no main effects were observed for the limb ($F_{1,13} = 0.342$, p = 0.569) and condition ($F_{1,13} = 2.498$, p = 0.138) variables regarding the ankle passive torque (Fig. 8-B). However, a main effect was observed for the angle variable ($F_{8,104} = 51.901$, p < 0.001). In both conditions, ankle passive torque significantly increased across all tested ROM (p < 0.01).

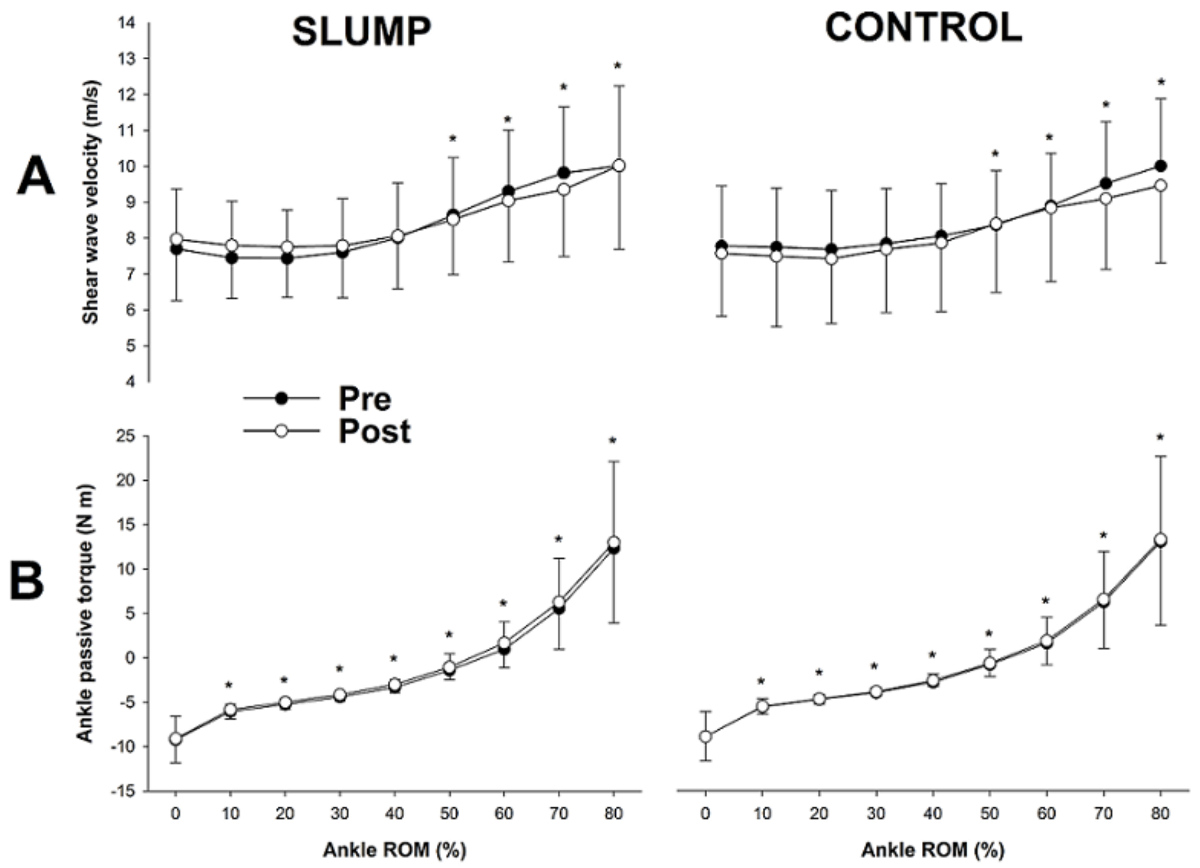

Figure 8. (A) Shear wave velocity of the sciatic nerve and (B) ankle passive torque during the ankle passive rotation from 40° of plantar flexion (0%) to 80% of maximal dorsiflexion range of motion (ROM) before (pre) and after (post) the slump and control interventions
* Statistical different from the initial ankle position (0% of ROM).

DISCUSSION

This study determined *in vivo* the acute effects of a slump technique on the stiffness of the sciatic nerve in healthy humans. We hypothesized that the slump intervention would induce an acute decrease of the sciatic nerve stiffness in healthy participants. This study showed that the sciatic nerve stiffness did not significantly change after 3 min of neural tension in a slump position.

Effects of slump on the sciatic stiffness

The findings from this investigation led us to reject the hypothesis that 3 min of the slump technique would result in a significant decrease of the sciatic SWV. Some explanations are proposed for these results. Firstly, we have noted that during the slump intervention some individuals did not reached full knee extension due to the low knee flexors stretch tolerance. It has been suggested that values of 29° of knee flexion (i.e. 0° corresponding to full knee extension) should be expected during the slump test, in healthy participants (Johnson and Chiarello 1997). Additionally, it was recently concluded that the sciatic nerve stiffness did not significantly increased during ankle dorsiflexion when the knee was remained flexed at 90° (Andrade et al. 2016). Thus, if participants have low knee flexors (i.e. mainly hamstrings and gastrocnemius) extensibility and are unable to reach full knee extension in a slump position, it will represent a mechanical limitation. Considering this, we hypothesize that starting the slump test sequence with the knee already in full extension (e.g. like the long-sitting position) may be more appropriate in order to apply more tension to the neuromuscular structures that surround the knee joint. Or, in alternative, the Straight Leg Raise test may also be contemplated as a neural tensioning technique, given that the test is always performed with full knee extension (Breig and Troup 1979), which may result in an increase of the sciatic nerve stiffness. However, these are only hypothesis based in insufficient data, and that have to be confirmed in future research. Secondly, biomechanical aspects of the sciatic nerve must be considered. Phillips et al. (2004) concluded, in animals, that the sciatic nerve presents heterogeneity of its tensile properties. In particular, the sciatic nerve is more compliant and has more strain in the regions close to joints, when compared to non-joint regions (Phillips et al. 2004), which means that the knee joint may play an important role in sciatic nerve tension. However, there is also one potential limitation regarding the SWV measurements. These were performed in just one site, described as a region with good for ultrasonographic visibility of the sciatic nerve, and where it was more superficial (Bruhn et al. 2008). Performing measurements in multiple sites along the nerve's path, including the sciatic nerve roots, would be relevant as it could provide more representative information regarding the stiffness of the whole nerve.

Effects of ankle ROM on the sciatic stiffness

The results from this study showed that the stiffness of the sciatic nerve becomes significantly higher as the ankle is rotated towards dorsiflexion. Specifically, significant changes in SWV were seen after 50 % of ankle ROM. This corresponds, in average, to 2° of plantarflexion, which means that this may be the point where the sciatic nerve starts to build up more tension during ankle dorsiflexion with the knee fully extended. This is consistent with the findings of Andrade et al. (2016) and Greening et al. (2016). Andrade et al. (2016) used an experimental setup similar to ours, and showed significant increases in the sciatic stiffness during ankle dorsiflexion, with the knee in full extension. In another structure, but with similar results, Greening et al. (2016) found a 136% increase in the tibial nerve SWV, when changed from a slack length position (i.e. hip and foot in neutral position, knee flexed at 90°) to a neural tension position (i.e. hip flexed, with the knee fully extended and the ankle dorsiflexed). These studies suggest that in order to induce neural tension, some segments must be placed in a specific position. In concrete, the stiffness of both the sciatic (Andrade et al. 2016), and tibial nerve (Greening et al. 2016), only increased when the knee was fully extended. Considering these results, it seems that knee extension has a decisive role in placing tension in the sciatic nerve.

Reliability of the sciatic SWV measurements

Nowadays, it is possible to reliably estimate the stiffness of peripheral nerves using shear wave elastography. We observed a substantial (Shrout 1998) intra-rater reliability (ICC=0.74-0.95; CV=3.4-8.9%) of the measurement of the sciatic nerve SWV during passive ankle dorsiflexion up to 80% of maximal ROM. Our results are somewhat consistent with previous studies results. Recently, similar CV values (< 8.0%), and slightly higher ICC values (0.92 - 0.98) were found (Andrade et al. 2016). Kantarci et al. (2014) measured the stiffness of the median nerve in a resting condition and found inter-rater reliability values similar to ours (ICC = 0.81 - 0.85). Also, the tibial nerve SWV was recently measured in a resting condition, with ICC values ranging from 0.37 to 0.54 (Greening et al. 2016). In addition, we observed a tendency for a lower reliability as the ankle dorsiflexion ROM increased. This is probably due to the building up of tension in all tissues surrounding the nerve (i.e. muscle and connective tissue), and also the nerve itself. The increase in tension may cause the transverse and superficial movements previously observed in the tibial and sciatic nerves, during ankle dorsiflexion and knee extension maneuvers (Boyd et al. 2012; Ridehalgh et al. 2014), affecting the reliability of the SWV measurement. Moreover, during SWV data processing, the increasingly higher stiffness levels of the sciatic nerve were observed in the elastogram as saturation points (i.e. values of SWV above the limit of the scale used). Although careful was taken in order to avoid these saturation points, during data processing, it is possible that this situation may still influenced the ICC values of the final ROMs. Considering this situation, we had to exclude 5 participants due to unfilled shear wave elastogram windows. We have noted that these participants had greater thickness of both the subcutaneous adipose tissue and the deep fascia. Altogether, this may act as a barrier for the supersonic push to travel through the deepest tissues, such as the sciatic nerve (i.e. in average located at a depth of 4-5 cm). The possible relation between the subcutaneous tissue and the SWV readings should be examined in a future study.

In this study we also calculated the MDD for every 10% increment in ankle ROM, starting with 40° of plantarflexion until 80% of ankle ROM. This parameter is of high clinical relevance because it can be used to determine whether a difference found between measurements may be interpreted as relevant or not (Weir 2005). Future investigations examining the sciatic nerve SWV in healthy population should consider these values as a reference for detecting, for instance, a relevant effect in consequence of a training intervention. However, the MDD of the sciatic nerve SWV assessment in clinical populations may present different values. Therefore future studies should investigate this issue.

CONCLUSIONS

This study showed that a sustained slump test position, which is often used in clinical and healthy populations with neural tensioning purposes, did not result in a decrease of the sciatic nerve stiffness, in healthy participants. These findings suggest that the benefits of neural tension techniques are not exclusively explained by alterations of the nerve mechanical properties.

Conflict of Interest

None to declare

Human Rights

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration.

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CHAPTER V - Sciatic nerve stiffness is increased in people with low back related leg pain and can be acutely reduced using a neural tension technique

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ABSTRACT

Background: Enlarged cross-sectional area has been found in the affected limb of people with low back related leg pain (LBRLP). However, it is unknown whether the sciatic nerve stiffness is altered in people with LBRLP; and if nerve tensioning techniques, commonly used in clinical practice, can change the sciatic nerve stiffness

Objectives: This study aimed to determine if the sciatic nerve stiffness is altered in people with LBRLP, and to examine the neural tension effects (i.e. slump position) on the sciatic nerve stiffness.

Methods: The sciatic nerve shear wave velocity (SWV, i.e. an index of stiffness) was measured in both legs of 16 participants (8 with unilateral LBRLP, and 8 healthy controls) during a passive ankle rotation, before, and immediately after 3 minutes of neural tension in a slump position. This protocol was applied in one limb, in the control group, and in the affected limb of the LBRLP group (randomized order).

Results: The affected limb of people with LBRLP showed higher sciatic nerve SWV (+11.3%, $P = 0.05$) when compared to the unaffected limb. No differences were observed to the healthy controls ($P = 0.34$). The nerve tension technique reduced the sciatic stiffness of the LBRLP affected limb (-10.2%, $P < 0.001$), with no changes in the unaffected limb ($P = 0.62$).

Conclusion: People with LBRLP have inter-limb differences in the sciatic nerve stiffness. This may be related with chronic alterations to the nerve mechanical properties, despite a nonsignificant difference found compared to healthy subjects. In addition, the stiffness asymmetry was restored after a nerve tensioning intervention.

Keywords: Neurodynamics; Peripheral nerve; Rehabilitation; Slump; Shear wave elastography

INTRODUCTION

People with low back related leg pain (LBRLP) often report diverse symptoms along the course of the sciatic nerve, extending sometimes below the knee (Konstantinou and Dunn 2008). Pain and numbness are the most frequent symptoms, but some neurologic signs like muscle weakness and reflex changes (e.g. knee or ankle reflex) may also occur (Ropper and Zafonte 2015). In addition, studies analyzing people with unilateral radiculopathy have observed an increased cross-sectional area of the affected nerve in comparison to the unaffected sciatic (Frost and Brown 2016; Kara et al. 2012). Another study showed that the transverse displacement direction of the sciatic nerve was altered in people with spinal referred leg pain (Ridehalgh, Moore, and Hough 2015). However, these studies do not provide information about the forces acting upon the nerves, mainly its stiffness. There is evidence that neural stiffness is altered in other peripheral neuropathies (Kantarci et al. 2014; Dikici et al. 2016), and this information can be a more valuable tool for the diagnosis of these pathologies than nerve morphology, or displacement, assessments. Nevertheless, there is currently no evidence if the sciatic stiffness is affected in people with LBRLP.

Moreover, neural tension tests, such as the slump test, have been used with the purpose of assessing mechanosensitivity of sciatic nerve (Butler 2000), by elongating the nerve bed at both ends. In addition, it has also been applied to rehabilitate people with lower back and/or sciatic nerve related problems (Maitland 1985). This practice is supported by *in vitro* experiments that reported changes in mechanical properties during and after a stretch stimulus (Driscoll, Glasby, and Lawson 2002). However, little is known about the actual effects of neural tensioning techniques performed *in vivo* on nerve properties. This is mainly due to the difficulty of assessing these properties non-invasively *in vivo*.

Recently, the shear wave elastography technique was proposed to reliably assess *in vivo* the nerve mechanical properties (Kantarci et al. 2014), based on the relation between shear wave velocity (SWV) and soft tissues stiffness (Bercoff et al., 2004; Eby et al. 2013). Andrade et al. 2016 showed that the sciatic nerve SWV is affected by both ankle and knee joint angles. In addition, the tibial nerve stiffness was reported to be higher in people with diabetic neuropathy (Dikici et al. 2016), as well as the median nerve stiffness in people with carpal tunnel syndrome (Kantarci et al. 2014). Thus, shear wave elastography can be used to examine differences in the nerve stiffness between clinical and healthy populations, and also to measure the mechanical effects of neural tension techniques.

Therefore, this study was designed: 1) to unravel whether the sciatic nerve stiffness is altered in people with history of LBRLP; and 2) to determine if a neural tension technique (3 min) in the slump position would change the sciatic nerve stiffness. We hypothesized that the sciatic nerve stiffness would be increased in the affected limb of people with LBRLP when compared to both the unaffected limb and healthy controls; and that a neural tension technique result in an immediate decrease of the sciatic nerve stiffness in the affected limb of people with LBRLP.

METHODS

Participants

Sixteen volunteers were invited to participate in this study (Table 1). Participants with LBRLP were included if the following criteria were present: 1) Males or females, aged between 18-45 years; 2) Body mass index < 30 kg/m^2; 3) non-acute unilateral presence of pain and/or numbness, originating in the lumbar spine, or buttock region, and traveling along the path of the sciatic nerve for more than 6 months [2]. Participants were excluded if they underwent spinal surgery, and if they presented an acute inflammatory state that prevented them to assume both the test, and the slump positions. Healthy participants were matched to the LBRLP participants regarding age, sex, height, weight, and did not reported any musculoskeletal problems, or neurologic deficits.

All participants read and signed the written informed consent accordingly to the Declaration of Helsinki. This study was approved by the Ethics Committee of the Faculdade de Motricidade Humana, Universidade de Lisboa (CEFMH Approval number: 3/2015).

Equipments and variables

Dynamometry

Passive ankle motion was executed by an isokinetic dynamometer (Biodex system 3 research, Shirley, NY, USA) at 2°/s. Ankle angle and torque were sampled at 1000 Hz (Biopac MP100 Acquisition System, Biopac Systems, Inc., Santa Barbara, CA, USA). Participants rested prone with the knee fully extended and the lateral malleolus aligned to the dynamometer axis (Fig. 9-A). The neutral position of the ankle (0°) was defined as the perpendicular position between the foot and leg, and determined by using an inclinometer.

Shear wave elastography

The procedures for the sciatic nerve SWV measurement were similar to previous studies from our group (Andrade et al., 2016). Briefly, an ultrasound scanner (Aixplorer, version

10.0; Supersonic Imagine, Aix-en-Provence, France) was used to assess (1 Hz) the sciatic SWV with a linear transducer array (SL 10-2 MHz, Super Linear 15-4, Vermon, Tours, France) in the muscular-skeletal preset (penetrate mode, smoothing level 9, and the persistence off). The maximal SWV scale value was set at 17.0 m/s. The sciatic nerve was first identified transversely (Fig. 9-B) by scanning the posterior thigh in B-mode, approximately 10 cm below the gluteal fold (Fig. 9-A). Then, the probe was orientated longitudinally until both superficial and deep epineurium of the nerve could be observed (Fig. 9-C). A waterproof marker was used to signalize the probe location in the skin, to ensure that measures were performed in the same location. Clip videos with both B-mode and shear wave elastography modes displayed were recorded during passive ankle dorsiflexion.

Electromyography

Surface electromyography (EMG) was used to record muscle activity using a telemetric system (Plux, Lisbon, Portugal). Surface electrodes (Ambu R BlueSensor N, Copenhagen, Denmark) were placed in the semitendinosus (ST), medial gastrocnemius (MG), and tibialis anterior (TA) mid-belly of both lower limbs, through guidance of ultrasound (B-mode). Signals were sampled at 1 kHz rate, amplified (x 1000) and digitized (8 - 500 Hz bandwidth) before analysis. EMG values were later normalized to the maximal isometric voluntary contraction (MIVC).

Clinical assessment

The Roland Morris Disability Questionnaire and the Oswestry Disability Index 2.0 were used to characterize the disability levels of the participants with LBRLP. The first consists in 24 items regarding the physical function (Roland and Morris 1983), which may be affected by LBRLP. The maximum score of the questionnaire is 24 (i.e. one per checked item) and translates into severe disability (Chiarotto et al. 2016). The Oswestry Disability Index 2.0 has 10 items that represent different health dimensions, from physical to social functioning (Fairbank and Pynsent 2000). The score is presented in percentage, resulting from adding the score of each applicable item, dividing it by the maximal total score, and multiplying by 100 (Chiarotto et al. 2016). Scores below or equal to 20% represent minimal disability; scores between 21 and 40% represent moderate disability; and results over 41% are associated with severe disability (Fairbank and Pynsent 2000). The intensity of pain was measured using a 10-point numeric rating scale. In addition, the duration of the symptomology was also registered.

Procedures

Participants visited the laboratory in one single session. After the clinical assessment, participants were positioned prone in the dynamometer table for the pre-intervention sciatic SWV assessment. The participants' maximal passive ankle dorsiflexion range of motion (RoM) was determined by using a hand-held stop button. The ankle movement was performed at 2°/s, and the participant voluntary stopped the dynamometer when they reached the point of stretching discomfort, and then the footplate immediately returned to a plantar flexion position. After this procedure, four plantarflexion-dorsiflexion cycles, starting from 40° of plantarflexion to the maximal dorsiflexion angle, were performed at 5°/s for conditioning purposes [16]. Thereafter, the SWV of the sciatic nerve and the ankle torque-angle were assessed in two maximal dorsiflexion RoM repetitions (2°/s). For the reliability analysis, the pre-intervention SWV measurements of the affected limb were used, and the probe was removed from the site of measurements and repositioned in the exact same location, between the two repetitions (1 min rest in between). All these procedures described were reproduced for both legs.

After the pre-intervention SWV measurements, the slump test sequence was performed on one limb (i.e., experimental limb), which was randomly chosen for healthy controls, and corresponded to the affected limb in the participants with LBRLP. Briefly, participants were seated with their hands behind the back, and were asked to flex their lumbar and thoracic spine into a slump position (Fig. 1-E). Afterwards, cervical spine flexion was added, and passively maintained in this position by an examiner. As the control limb stayed relaxed, the knee was passively extended by a second examiner, while the ankle was dorsiflexed until strong resistance was felt by the examiner, or if the participant reported pain or discomfort. This position was statically maintained during 3 min.

Immediately after the slump protocol, participants were re-positioned in prone for the post-intervention SWV assessment, which was always performed first in the limb subjected to the intervention. Finally, for EMG normalization, 2 MIVC repetitions (1 min rest between repetitions) were performed for plantarflexors, dorsiflexors, and knee flexors muscles of both limbs.

Data processing

Data acquisition was synchronized by using an external trigger recorded using a Biopac MP100 Acquisition System (Biopac Systems, Inc., Santa Barbara, CA, USA), and processed using customized Matlab routines (The Mathworks, Natick, USA). Briefly, in the sonograms clips, the sciatic region of interest was determined by selecting the largest area within the epineurium in the elastogram window (Fig. 9-C and 9-D). This procedure was repeated for each frame (i.e. every second), to ensure that the region of interest would not be affected by the nerve motion during the maneuvers. When selecting the region of interest, careful was taken to avoid regions of saturation (i.e. values higher than the ones supported by the ultrasound device). The color pixels were converted to SWV values according to the scale used, and their average was determined to use for statistical analysis. The sonograms clips with incomplete elastogram windows were excluded from analysis.

As the ankle maximal ROM was different between the participants, the ankle angles were normalized to the maximal ROM. Ankle range until 80% of maximal ROM was considered for analysis. This ROM cut-off was also used in a previous study (Andrade et al. 2016) since the elastogram in some participants reaches the maximal value of the scale (i.e. 17 m/s), and considerable artifacts occurs above this ankle ROM.

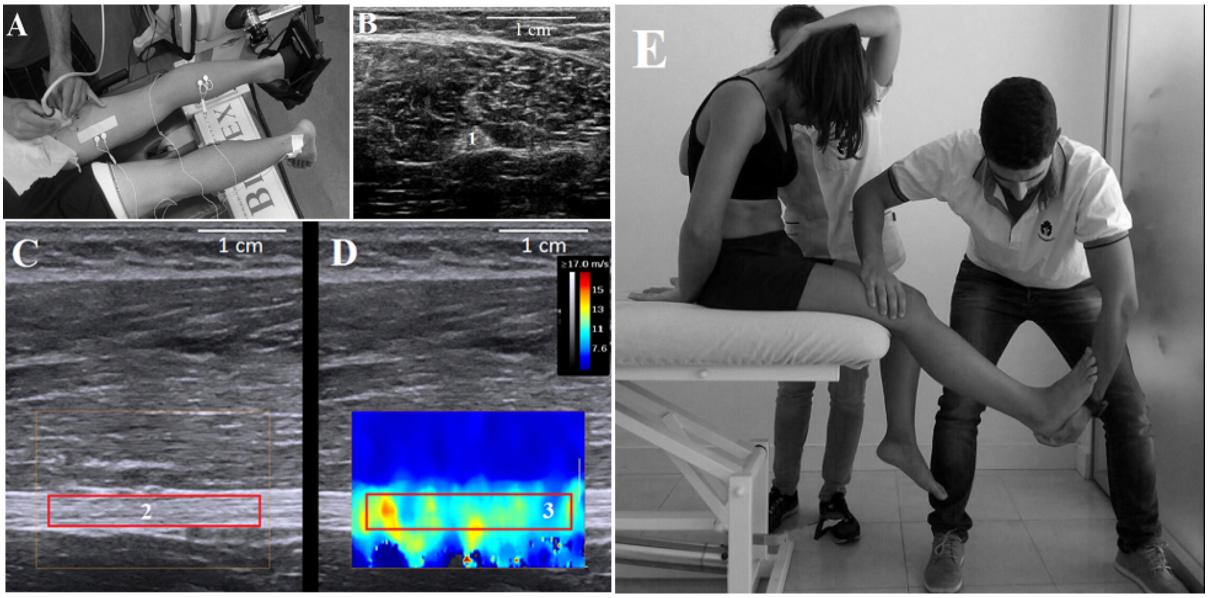

Figure 9. A – Experimental setup; B – Cross-sectional view of the sciatic nerve (1) in B-mode; C – Longitudinal view of the sciatic nerve in B-mode; D – Elastogram window was defined above the nerve section, and the largest area within the epineurium was considered as region of interest (2) and (3); E – Example of the intervention in a slump position.

Statistical Analysis

The number of participants for this study was determined using the software G*Power 3.0.10 (Erdfelder et al. 1996). Using an alpha of 0.05, a power of 0.9, a correlation among repetitions of 0.85, and an estimated effect size of 0.3 (correlation and effect size were determined using data from a previous pilot study), a total sample of 12 participants (i.e. 6 by group) was determined. This number was increased to 16 (i.e. 8 by group) in anticipation for dropouts or missing data.

Descriptive statistics (e.g. mean and standard deviation) were used for sample characterization. A t-test for independent samples was used to assess the differences between groups regarding demographic variables (e.g. age, weight, height, BMI).

Reliability measures of the shear wave velocity assessment included the intraclass coefficient correlation ($ICC_{2,1}$), the standard error of measurement (SEM), the minimal detectable difference (MDD). The SEM was calculated as follows: $SEM = \sqrt{MS_E}$, where MS_E represents the error mean square, obtained from the 2-way random effects analysis of variance. The MDD was determined by the formula $MDD = SEM \times 1.96 \times \sqrt{2}$ (Weir 2005). The SEM and MDD were also normalized to the SWV.

Data were tested for normality using the Shapiro-Wilk test, and no serious violations from normality were noted. A 2-way repeated measures ANOVA [limb (control, experimental) × ankle ROM (0, 10, 20, 30, 40, 50, 60, 70, and 80 % of maximal ROM)] was carried out for each group, in order to compare the pre-intervention SWV between limbs, throughout the ankle ROM. A 2-way mixed ANOVA [group (LBRLP, healthy controls) x ankle ROM (0, 10, 20, 30, 40, 50, 60, 70, and 80 % of maximal ROM)] was performed to assess the difference between the groups in the pre-intervention SWV, throughout the ankle ROM, for each limb (e.g. LBRLP affected limb *vs* healthy experimental limb, and LBRLP unaffected limb *vs* healthy control limb). A 3-way repeated measures ANOVA [limb (control, experimental) × ankle ROM (0, 10, 20, 30, 40, 50, 60, 70, and 80 % of maximal ROM) × condition (pre, post)] was performed to determine the effects of the slump intervention in the SWV of the sciatic nerve and in the ankle passive torque, of each group. In all the ANOVAs, the additional assumption of sphericity was assessed with Mauchly's test and when it was violated, the degrees of freedom were corrected using Greenhouse-Geisser estimates. The Eta Squared (η^2), obtained from the repeated measures ANOVA was used as an estimate of effect size, and it was determined using the following formula: $\eta^2 = SS_{between} / SS_{total}$, where $SS_{between}$ represents the sum of squares for the effect of interest, and SS_{total} represents the total sum of squares (Levine 2002). Statistical significance was set at 0.05. The IBM SPSS software (version 21.0, IBM Corporation, NewYork, USA) was used for the statistical analysis.

RESULTS

Demographic variables are reported in Table 5. No significant differences were found between LBRLP and healthy participants. Clinical characteristics of the LBRLP participants are presented in Table 6.

Table 5. Demographic variables from LBRLP and healthy participants

	LBRLP group, n = 8	Control group, n = 8	p-value
Sex (male/female)	6/2	5/3	-
Age (years)	30.8 ± 7.4	28.1 ± 8.3	0.517
Weight (kg)	74.7 ± 8.2	68.1 ± 11.3	0.204
Height (m)	1.77 ± 0.08	1.73 ± 0.11	0.386
BMI (kg/m^2)	23.7 ± 1.5	22.6 ± 1.6	0.182
Dorsiflexion ROM (°)	33.5 ± 7.1	34.4 ± 7.5	0.814

Values are mean ± standard deviation. BMI – Body mass index; ROM – Range of motion.

Table 6. Clinical variables of the participants with LBRLP (n=8)

Participant number	1	2	3	4	5	6	7	8	Mean ± SD
Sex	M	M	F	F	M	M	M	M	-
RMQ (0-24)	8	8	4	6	6	4	7	2	5.6 ± 2.1
ODI (%)	20	14	18	26	24	4	20	10	17.0 ± 7.3
Duration of symptoms (months)	36	12	156	12	24	60	96	240	79.5 (81.4)
Pain (10-point NRS)	5	4	1	5	2	2	6	4	3.6 ± 1.8

F – Female; M – Male; NRS – Numeric Rating Scale; ODI – Oswestry Disability Index; RMQ – Roland Morris Disability Questionnaire; SD – Standard deviation.

The reliability outcomes of the SWV assessment are detailed in Table 7, in Appendix. The SWV measurements revealed substantial intra-rater reliability, with ICC values ranging from 0.83 (CI: 0.47 - 0.96) at 20% of maximal ROM and 0.99 (CI: 0.95 - 0.99) at 0% of maximal ROM. The average SEM across the ankle percentiles was 0.7 ± 0.3 m/s, and the average MDD was 1.9 ± 0.8 m/s.

Sciatic SWV of LBRLP and healthy participants

During all the SWV measurements, a 1.6% ± 0.8%, 1.9% ± 0.9%, and 2.8% ± 2.1% of muscle activation were observed for the semitendinosus, medial gastrocnemius, and tibialis anterior muscles, respectively.

An example of the curve SWV *vs* ankle ROM for both the affected and unaffected limbs of a LBRLP participant is shown in Figure 10. Detailed information about the sciatic SWV, throughout the ankle ROM percentiles in both groups is shown in Table 8, in Appendix.

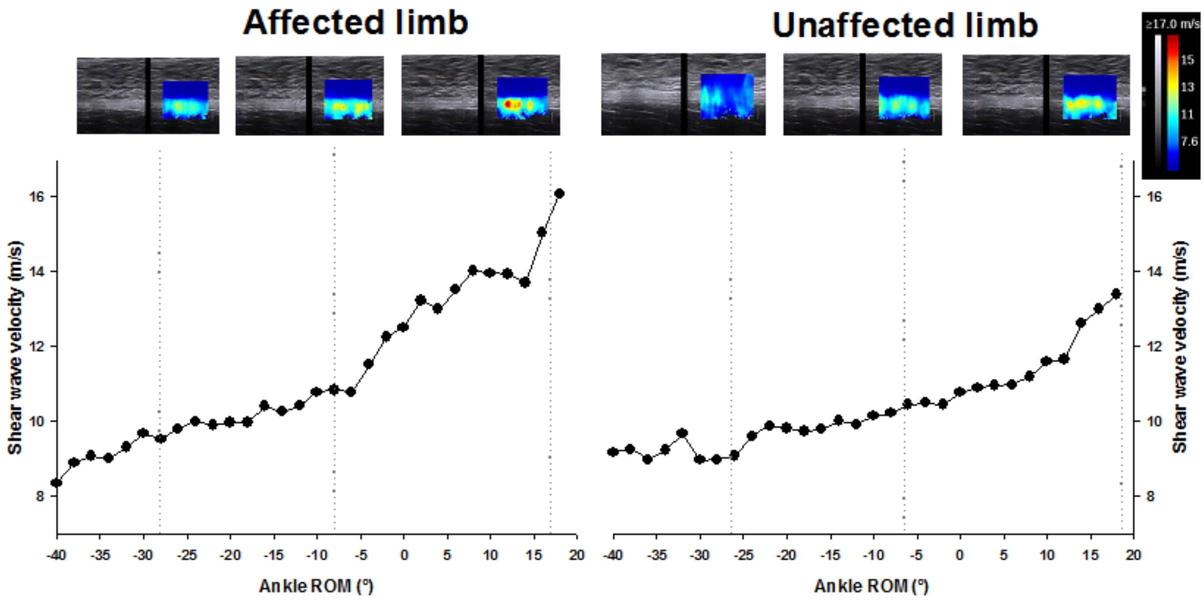

Figure 10. Sciatic shear wave velocity response during an ankle dorsiflexion, in both the affected (left image) and unaffected (right image) limbs of one participant (#7) with low back related leg pain. For each graphic examples of the elastogram are provided for 3 different amplitudes, 30° and 10° of plantarflexion, and 15° of dorsiflexion.

Figure 11 represents the SWV throughout the ankle RoM of the two lower limbs in both groups, for the pre-intervention condition.

Concerning the within-subjects analysis, no significant interaction (limb × ankle ROM) was observed, but a significant main effect was found for limb ($F_{1,7}$ = 5.623, *P* = 0.050) in the LBRLP group. The affected limb showed, in average, more 11.3% of SWV compared to the unaffected limb. In the healthy group, neither significant interactions (limb × ankle ROM) nor limb effect ($F_{1,7}$ = 0.213, *P* = 0.658) were found.

Regarding the between-group analysis, no significant interactions (group × ankle ROM), and no significant group effect was detected, for both legs. When the SWV of the affected limb of people with LBRLP and the experimental limb of healthy people were compared, the result was $F_{1,14}$ = 0.995, P = 0.336; when the SWV of the unaffected limb of the LBRLP participants was compared with the control limb of healthy participants, the result was $F_{1,14}$ = 0.025, P = 0.878.

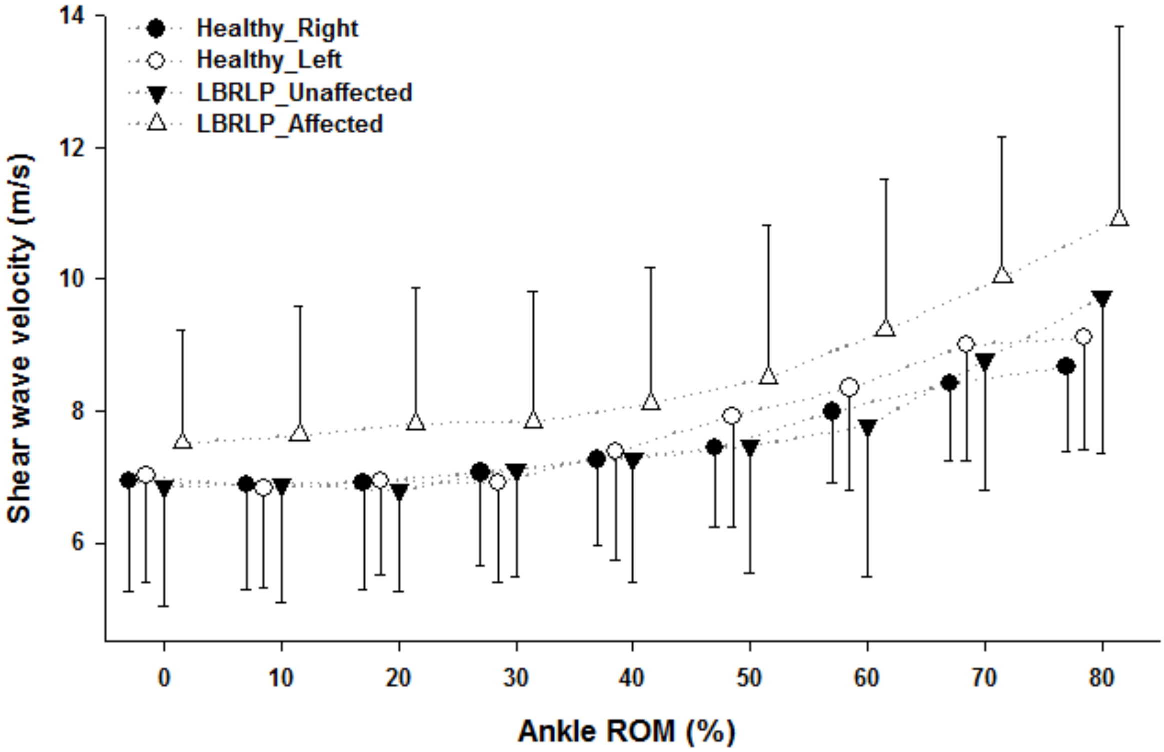

Figure 11. Between-groups and within-subjects comparisons of the sciatic shear wave velocity (mean ± SD) throughout the ankle motion percentiles for the pre-intervention condition. Significant differences were found between the affected and unaffected limbs of the LBRLP group.

Effects of the slump intervention

Figure 12 shows the effects of slump intervention on the sciatic SWV throughout the ankle motion in lower limbs of both groups. More detailed information can be found in Table 3, in appendix.

For the SWV analysis, in people with LBRLP (Fig. 4), no significant 3-way interaction (limb × ankle ROM × condition) was observed, but both 2-way interaction related with condition (limb × condition, and ankle ROM × condition) were significant. Then separated 2-way repeated measures ANOVA [ankle RoM (0, 10, 20, 30, 40, 50, 60, 70, and 80% of maximal ROM) × condition (pre, post)] by limb were carried out. In the experimental limb, no significant interaction (ankle ROM × condition) was observed, but a significant main effect was found for condition ($F_{1,7}$ = 41.037, P < 0.001). Specifically, the neural tension intervention significantly reduced the sciatic nerve stiffness by 10.2%. In the control limb, neither significant interaction (ankle ROM × condition) nor condition effect ($F_{1,7}$ = 0.273, P = 0.617) were found.

In the healthy group (Fig. 4), neither 3-way interaction (limb × ankle ROM × condition) nor any of the 2-way interactions were significant. Also, no main effects were found for limb or condition.

Similar analysis was done for the ankle dorsiflexion passive torque. In people with LBRLP, neither 3-way interaction (limb × ankle ROM × condition) nor any of the 2-way interactions were significant. In addition, no main effects were found for limb or condition.

In the healthy group, no significant 3-way interaction (limb × ankle RoM × condition) was observed, but 2-way interaction (limb × ankle ROM) was significant. Then separated 2-way repeated measures ANOVA [angle (0, 10, 20, 30, 40, 50, 60, 70, and 80 % of maximal ROM) × condition (pre, post)] by limb were carried out. For both experimental and control limbs, neither significant interaction (ankle ROM × condition) nor condition effect [$F_{1,7}$ = 0.010, P = 0.924 (experimental limb), $F_{1,7}$ = 0.020, P = 0.892 (control limb)] were found.

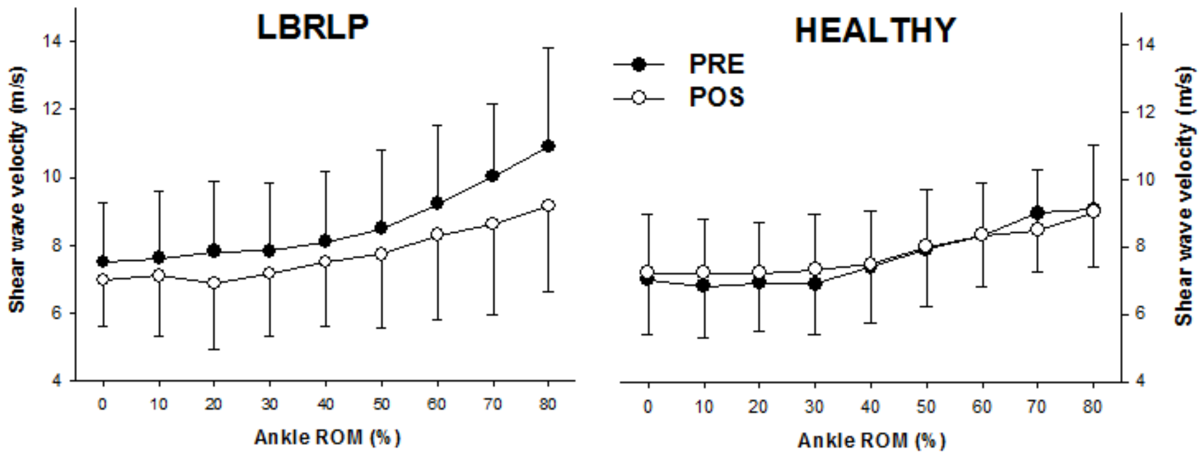

Figure 12. Sciatic shear wave velocity (mean ± SD) before (PRE) and after (POS) the slump intervention, of the LBRLP and HEALTHY participants.Significant differences were found between the PRE and POS shear wave velocity measurements, in the LBRLP group.

DISCUSSION

In this study, we showed that the sciatic nerve of the LBRLP affected limb presented a higher stiffness than the unaffected limb, confirming our hypothesis of inter-limb differences regarding the sciatic stiffness. However, contrary to our hypothesis we did not observe differences in the sciatic stiffness between people with LBRLP and the control group. In addition, we also confirmed the hypothesis that a static neural tension intervention would immediately reduce the sciatic stiffness of the affected limb of the LBRLP participants.

Sciatic stiffness in LBRLP and Healthy people

Literature shows that some neuropathies can affect the mechanical properties of peripheral nerves (Boyd et al. 2012; Lopes et al. 2011). For instance, Hough et al. (2007) concluded that people with carpal tunnel syndrome exhibit a lower longitudinal nerve excursion, whereas others have reported increased nerve stiffness measured using SWE (Kantarci et al. 2014). In respect to people with LBRLP, two studies reported a significant increase in the sciatic nerve cross-sectional area of the affected limb, when compared to the unaffected limb (Frost and Brown 2016; Kara et al. 2012). Additionally, Ridehalgh et al. (2015) observed that the sciatic nerve moved medially during the passive straight leg raise, compared to healthy controls where the nerve moved laterally (Ridehalgh et al. 2015). However, none of these investigations measured the sciatic nerve stiffness in people with LBRLP. In the present study, we observed that the sciatic nerve stiffness (i.e. SWV) was higher in the affected limb compared to the unaffected, which is in direction with the conclusions of the previous studies that analyzed the sciatic nerve properties in people with LBRLP. An explanation for these results may be found in previous research, which shown that persistent endoneural edema, as a result of constant mechanical aggressions, leads to intraneural fibrosis (Millesi et al. 1995; Rempel et al. 1999). Assuming that the (affected) nerves of LBRLP may be under chronic stress due to the mechanical etiology, we hypothesize that the nerve viscoelastic properties could be compromised, which may result in increased nerve stiffness. However, future studies may want to examine if the asymmetries found between limbs in people with LBRLP are related to a mechanical etiology, and if this evolves as the pathological condition progresses.

Moreover, we observed no significant differences in the sciatic stiffness between LBRLP and healthy people. However, when we looked specifically to the difference in the sciatic SWV throughout each ankle ROM percentile, we noticed that only in 2 out of the total 9 percentiles the between-group difference of SWV was inferior to the SEM (i.e. percentiles 20% and 50%, please see in Table 7 and 8, in Appendix). This suggests that the between-group difference may not be solely explained by the error of measurement, indicating possible effects of the pathology. Interestingly, Frost and Brown (2016) measured the sciatic nerve CSA in people with mild (mean ODI score: 19.9%) and chronic (mean symptom duration: 126 months) unilateral LBRLP, and also found between-limbs differences, but not when compared to healthy controls. Our results, together with the ones reported by Frost and

Brown (2016), strengthen the hypothesis that the absence of between-groups differences may be due to a high variability that naturally occurs in the sciatic stiffness of healthy men and women. The minimal levels of disability reported by the participants with LBRLP may also explain this result. Eventually, people with more severe symptomatology and with longer durations, may present higher sciatic stiffness. In addition, we only measured the sciatic SWV in one site, which was described as a location with good ultrasonic visibility and where the nerve was more superficial (Bruhn et al. 2008). It would be relevant to have stiffness measures closer to the nerve roots. Considering that the majority of LBRLP conditions are related to compression or inflammatory processes in the nerve root regions, assessing stiffness in this area might yeld even greater differences in the sciatic stiffness. Therefore, a future study should examine different proximal and distal sites to the one used in this study. We hypothesize that measurements close to the nerve roots of the sciatic nerve would yield even higher SWV values. However, this should be confirmed in future research, together with the influence of different levels of self-reported disability in the mechanical properties of peripheral nerves. Furthermore, it would be of high clinical value if future studies aimed at establishing cutoff values for sciatic SWV in people with LBRLP.

Effect of the Slump intervention in the sciatic stiffness

Neural tension interventions in a Slump position are frequently used by health professionals, mainly physiotherapists, to target the lower limb nerve tract (Cleland et al. 2006; Nagrale et al. 2012). Thus, we showed that a sustained neural tension position acutely reduce the sciatic stiffness of the affected limb of LBRLP people. The effects of tension in peripheral nerves are known, mostly due to research conducted in animal models (Driscoll et al. 2002; Kwan et al. 1992) and human cadavers (Byl et al. 2002; Coppieters et al. 2006). It is well known that nerves have viscoelastic characteristics when subjected to loading (Driscoll et al. 2002). Initial deformation of peripheral nerves requires small loads, and as the elongation increases, higher loads are necessary to deform the nerve until the point of failure (Rydevik et al. 1990). Experiments in the tibial nerve of rats have shown a 30% stress relaxation occurring within the first 5 min of static stretch (Kwan et al. 1992). The explanation for this phenomenon may be related to the intraneural fluid shifts which occur in response to tensile loading (Kendall et al. 1979).

Until few years ago, there was little human *in vivo* information regarding the mechanical behavior of peripheral nerves subjected to tension stresses. Shear wave elastography allows to assess *in vivo* the stiffness of peripheral nerves, based on the relation between SWV and soft tissues stiffness (Eby et al. 2013). We observed in this study a ~10.2 % decrease in the sciatic nerve stiffness of the affected limb, after the slump intervention. It has been reported that prolonged compressive forces acting upon the nerve, as the one related with nerve root compression, result in endoneurial edema (Powell and Myers 1986). If this compression is maintained for long periods, the edema will cause a pressure increase enough to impair blood flow, leading to ischemic damage to capillary endothelial cells and changes to the blood-nerve barrier (Dahlin and McLean 1986; Dyck et al. 1990). Considering the chronic nature of the LBRLP symptoms (i.e. > 1 year), we hypothesize that the sciatic nerve of the affected limb may present some of these physiological alterations, such as endoneurial edema. Neurodynamics techniques have been associated with intraneural blood flow facilitation (Wang et al. 2015) which favors intraneural fluid dispersion (Gilbert et al. 2015) possibly leading to the sciatic stiffness reduction observed in this study. However, it is not clear if this mechanical adaptation translates into clinical enhancements, such as pain relief, or improved mechanosensitivity. Therefore, it is very important that future studies using longitudinal designs, and larger samples, try to establish the relationship between the mechanical and clinical effects of neurodynamics that apply tension to the sciatic, such as a sustained slump position.

It is important to note two methodological aspects of this study. First, the LBRLP participants presented heterogeneity in the duration of the symptoms (i.e. ranging from 1 year to 20). This could be interpreted as a limitation, given that it is unclear whether this heterogeneity reflects on the sciatic mechanical properties. Secondly, only one post intervention measurement of the sciatic stiffness was performed. It would be relevant to analyze the time course of the neural tension effects, by performing additional assessments (e.g. at 10, 30, and 60 min after the intervention), to determine if, and when, the stiffness returns to baseline.

CONCLUSIONS

This study provides evidence of inter-limb differences regarding sciatic stiffness, in people with low back related leg pain. This may indicate chronic changes to the nerve mechanical properties, despite a nonsignificant difference found to healthy subjects. Additionally, the stiffness of affected sciatic nerves of people with low back related leg pain was reduced immediately following neural tension in a slump position. This supports the use of this technique to acutely restore neural stiffness. Future studies in this clinical population should explore the chronic effects of this type of intervention on nerve mechanical properties.

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APPENDIX

Table 7. Reproducibility of the SWV measurements in LBRLP people

%ROM	ICC	CI	SEM	MDD
0	0.99	[0.95-0.99]	0.26	0.71
10	0.96	[0.86-0.99]	0.46	1.28
20	0.83	[0.47-0.96]	1.07	2.97
30	0.97	[0.88-0.99]	0.45	1.24
40	0.96	{0.85-0.99]	0.52	1.44
50	0.96	[0.84-0.99]	0.59	1.63
60	0.92	[0.7-0.98]	0.85	2.37
70	0.91	[0.68-0.98]	0.86	2.38
80	0.91	[0.67-0.98]	1.06	2.93

ROM – Range of motion; ICC – Intraclass correlation coefficient;
CI – Confidence interval; SEM – Standard error of measurement;
MDD – Minimal detectable difference

Table 8. Within-group, and between-groups, difference of sciatic SWV before the intervention, throughout the ankle ROM percentiles

	LBRLP						HEALTHY						LBRLP vs HEALTHY					
%ROM	Affected	SD	Unaff.	SD	Difference	ES	Control	SD	Exp.	SD	Difference	ES	LBRLP	SD	HEALTHY	SD	Difference	ES
0	6.85	1.81	7.51	1.73	-0.66	-0.37	6.93	1.65	7.02	1.63	-0.09	-0.06	7.51	1.73	7.02	1.63	0.49	0.29
10	6.89	1.81	7.62	1.96	-0.73	-0.39	6.89	1.61	6.82	1.50	0.06	0.04	7.62	1.96	6.82	1.50	0.80	0.46
20	6.79	1.54	7.81	2.07	-1.03	-0.57	6.91	1.64	6.93	1.43	-0.01	-0.01	7.81	2.07	6.93	1.43	0.88	0.51
30	7.12	1.64	7.82	2.00	-0.70	-0.39	7.06	1.42	6.91	1.51	0.15	0.10	7.82	2.00	6.91	1.51	0.91	0.52
40	7.27	1.88	8.11	2.07	-0.83	-0.42	7.26	1.30	7.38	1.65	-0.12	-0.08	8.11	2.07	7.38	1.65	0.73	0.39
50	7.46	1.92	8.49	2.32	-1.03	-0.48	7.43	1.19	7.92	1.69	-0.49	-0.34	8.49	2.32	7.92	1.69	0.57	0.28
60	7.77	2.29	9.22	2.30	-1.45	-0.63	7.98	1.06	8.34	1.54	-0.36	-0.28	9.22	2.30	8.34	1.54	0.88	0.46
70	8.77	1.97	10.03	2.12	-1.26	-0.62	8.41	1.16	9.00	1.74	-0.59	-0.41	10.03	2.12	9.00	1.74	1.03	0.53
80	9.73	2.37	10.91	2.92	-1.18	-0.45	8.67	1.28	9.11	1.70	-0.44	-0.30	10.91	2.92	9.11	1.70	1.80	0.78

SD – Standard deviation; ES – Effect size; LBRLP – Low back related leg pain group

Table 9. Sciatic shear wave velocity, before (PRE) and after (POS) the intervention, in both groups, and associated effect size

	LBRLP						HEALTHY					
%ROM	PRE	SD	POS	SD	Difference	ES	PRE	SD	POS	SD	Difference	ES
0	7.51	1.73	6.97	1.36	0.54	0.35	7.02	1.63	7.21	1.76	-0.19	-0.11
10	7.62	1.96	7.10	1.79	0.53	0.28	6.82	1.50	7.23	1.58	-0.40	-0.26
20	7.81	2.07	6.86	1.93	0.96	0.48	6.93	1.43	7.21	1.50	-0.28	-0.19
30	7.82	2.00	7.16	1.86	0.66	0.34	6.91	1.51	7.31	1.66	-0.40	-0.25
40	8.11	2.07	7.49	1.89	0.62	0.31	7.38	1.65	7.48	1.59	-0.10	-0.06
50	8.49	2.32	7.72	2.18	0.77	0.34	7.92	1.69	8.00	1.68	-0.08	-0.05
60	9.22	2.30	8.30	2.49	0.93	0.39	8.34	1.54	8.34	1.57	0.00	0.00
70	10.03	2.12	8.60	2.68	1.42	0.59	9.00	1.74	8.49	1.82	0.51	0.29
80	10.91	2.92	9.16	2.54	1.76	0.64	9.11	1.70	9.02	2.01	0.09	0.05

SD – Standard deviation; ES – Effect size

CHAPTER VI - General Discussion

The development of this thesis was prompted by a lack of knowledge identified in the literature, regarding the mechanical effects of neurodynamics techniques. Neurodynamics is commonly used by health professionals, mainly physiotherapists, for the purpose of evaluation and treatment of a variety of neuromuscular disorders. There was an empirical notion from the clinical practice that these techniques promoted functional outcomes, however proper evidence of such effects in the lower body quadrant did not exist. In addition, there was no evidence about the mechanical/physiological changes related to the effects of neurodynamics. Consequently, this thesis aimed at determining the acute effects of neurodynamics maneuvers, specifically neural tension, in the stiffness of the sciatic nerve, in both healthy participants and people with LBRLP. Another purpose of this thesis was to analyze if people with LBRLP presented baseline changes in the sciatic nerve stiffness, which could be associated with adaptations in the neural tissues following chronic symptomatology, as seen in other neuropathies (Kantarci et al., 2014). To address these objectives, 3 studies were carried out. Their main findings will next be summarized, while providing a discussion that joins together the 3 studies. The practical implications of these results will be debated, as well as the limitations of this thesis and recommendations for future research.

1. Summary of main findings

The main results of this thesis showed that neurodynamics interventions directed to the lower body quadrant have a positive impact in both healthy and clinical populations (i.e. people with low back pain). It was also observed, in people with unilateral LBRLP, that the sciatic stiffness of the affected limb was significantly increased, and that a neural tension technique produced an acute reduction in its stiffness. These results aid to accomplish the objectives defined in the Introduction, and also support the hypothesis formulated in this thesis.

The first study of this thesis was a systematic review, with meta-analysis, which examined 10 studies. Results from the meta-analysis support the hypothesis that the use of neurodynamics techniques would yielded large effect sizes, in both populations. Although few studies were included for each variable (along with other limitations discussed in the Chapter III), this systematic review provides clear evidence of the benefits of using neurodynamics in pain relief, disability improvement, and flexibility augments. Other systematic reviews (Ellis & Hing, 2008; Su & Lim, 2015) have analyzed the effects of neurodynamics, but the majority of the conclusions were about its effects on upper body quadrant, exclusively in clinical populations. We examined the effects of neurodynamics applied specifically to the lower body quadrant, both in healthy people and in people with LBP. However, there is no consensus regarding the ideal parameters for applying neurodynamics, which is the product of the high heterogeneity found in this review, and reported also in other reviews. The development of clinical guidelines or recommendations is hampered by this heterogeneity. Only more research, testing the efficacy of different parameters, can define which is the appropriate load and duration of neurodynamics interventions. Nevertheless, the question regarding the physiological mechanisms underlying the effects of neurodynamics remained unanswered. Studies 2 and 3 were conducted in order to address that question.

In the second study we used a quasi-experimental design to investigate the immediate effects of a neurodynamics intervention in healthy people. The intervention was selected accordingly to the information collected in the systematic review concerning the most common neurodynamics techniques and respective parameters. Despite the heterogeneity in the neurodynamics parameters, a nerve tension intervention in the slump position was adopted, with the hypothesis of creating more impact on the sciatic stiffness. The neurodynamics intervention had a duration of 3 min, which was intentionally superior to the ones found in the review, in order to assure time enough to induce any eventual change in the sciatic SWV. Results from the study showed that a neural tension intervention in a slump position did not significantly change the stiffness of the sciatic nerve, leading us to reject the hypothesis that this technique would result in an immediate decrease of the sciatic stiffness in healthy people. Several explanations were discussed in Chapter IV to justify this finding, but we highlight the importance of the knee position during the intervention, which we believe to have a decisive role in adding tension to the sciatic nerve. It has been shown that knee extension deficits during the slump test are related to the tension of the surrounding tissues (Butler, 1989). Butler (1989) considers the popliteal region as a neural tissue tension point, where both the sciatic and the tibial nerves converge during knee extension. Therefore, we hypothesize that neurodynamics techniques that assume a full knee extension (e.g. SLR) may be more effective in applying tensile loads to the sciatic nerve. Nevertheless, this should be confirmed in future research.

Regarding the third study, it was observed that people with unilateral LBRLP have an alteration in the sciatic nerve stiffness. When compared to the unaffected limb, the sciatic nerve of the affected limb exhibited higher SWV values. However, there were no differences in the sciatic stiffness of the affected limb of people with LBRLP when compared to either limb of the healthy participants. Our results are in agreement with another study (Kantarci et al., 2014) which reported differences in the median nerve stiffness between the affected and unaffected limbs, in people with carpal tunnel syndrome. In addition, other studies performed in people with LBRLP (Frost & Brown, 2016; Kara et al., 2012) also support our findings. In these studies, the CSA of the sciatic nerve was measured, and it was concluded that the affected limb presented higher CSA than the unaffected limb. It is possible that this change in the nerve morphology is related to our findings relative to the sciatic nerve stiffness increase, indicating that nerves may undergo mechanical adaptations following chronic adverse conditions. Future research should confirm this hypothesis. Regarding the absence of difference in the sciatic nerve stiffness between healthy people and people with LBRLP, similar results were obtained by Frost & Brown, (2016). As discussed in chapter V, this finding may be related to the high variability in the stiffness of healthy sciatic nerves, and also to the minimal levels of disability reported by both studies' populations.

Another important finding from the third study is related with the acute effects of the neural tension intervention in significantly reducing the sciatic nerve stiffness of the affected limb, in people with LBRLP. Considering that this same intervention did not produce similar effects in healthy participants, it is possible that this effect of neural tension is related with changes in the sciatic nerve mechanical properties, in people with unilateral LBRLP, which make the neural tissue more compliant to neurodynamics interventions. If we consider the pathophysiological and pathomechanical consequences of nerve injury, we realize that several components are affected, such as the vascular supply, connective tissue, or nerve conduction (Nee & Butler, 2006). In addition, tissues surrounding the nerve may also be affected, which altogether leads to mechanosensitivity of the peripheral nerves (Takahashi, Yabuki, Aoki, & Kikuchi, 2003). It is considered that intraneural blood flow is one of the first aspects to be compromised during repetitive forces that exceed the nerve capacity to withstand physical stresses (Rempel, Dahlin, & Lundborg, 1999). As seen earlier in the literature review (chapter II - *Peripheral nerve anatomy*) there is a vast and dense capillary network supplying the peripheral nerves, which helps to regulate a proper intraneural pressure (Sunderland, 1978). A change to this equilibrium will cause a persistent endoneurial edema that will lead to intraneural fibrosis. If this situation is maintained the viscoelastic properties of neural tissues will be affected (Millesi et al., 1995), which would explain the higher sciatic stiffness of the affected limb, in people with LBRLP. Thus, inter-limb differences in the sciatic stiffness are to be expected if the reported symptoms have a long duration. Likewise, when the mechanical properties of the peripheral nerves are altered, interventions specifically targeting these structures and their mechanical interface should help to restore proper neurodynamics.

2. Limitations and recommendations for future research

The limitations of each individual study have already been discussed in the respective chapters. There are however some general limitations mainly attributed to methodological aspects, concerning both the studies 2 and 3. One limitation is related with the absence of measurement of the knee angle during the slump intervention. As observed in studies 2 and 3, most subjects did not perform full knee extension, and it would be interesting to measure that knee extension deficit. Future studies could determine if eventually knee ROM restrictions are correlated with the sciatic stiffness. Furthermore, the results of this thesis should be limited to the population with mild and chronic symptomatology of unilateral LBRLP. Possibly, more severe or acute stages of this clinical condition may yield different results. In addition, we included both people with radicular pain, and radiculopathy. These two conditions have often been studied together under the category of low back related leg pain (Cook, 2009; Spijker-Huiges et al., 2015), but we acknowledge that both represent different pathological conditions with distinct symptomatology, and should, in future research, be investigated separately.

Our recommendations for future research are based in four main ideas, which we believe to be of scientific and clinical relevance. First, this thesis showed a reduction in the sciatic stiffness immediately following the neural tension intervention. It would be relevant to perform a time-course analysis to this effect, and to determine when it resumed the baseline values. Also, as previously mentioned, research should establish cutoff values for the stiffness of the sciatic nerve. This information would be valuable for health professionals to make a more precise diagnosis. Finally, many studies use either neural tension or neural gliding techniques to improve neurodynamics of clinical populations. Some studies have compared the clinical effects of neural tension or neural gliding techniques, yet to our knowledge no studies have compared its mechanical effects on the sciatic nerve. Some authors defend the use of neural gliding exercises with the assumption that they imply smaller stress to the neural structure, but there are no *in vivo* studies to support these claims. Consequently, it would be relevant to determine the effects of neural gliding maneuvers in the sciatic mechanical properties, and to compare it to neural tension interventions.

The results from this thesis may provide some insight for the use of neurodynamics by health professionals, mainly physical therapists, in a variety of clinical contexts. Next, the practical implications of such findings will be discussed.

3. Implications for clinical practice

3.1. Evidence-based supporting the use of neurodynamics techniques

The observed findings from this thesis not only provide evidence of the clinical and mechanical effects of neurodynamics, but also highlight the importance of a thorough understanding of the forces acting upon the peripheral nervous system. As seen in the literature review (Chapter II - *Peripheral nerves biomechanics*) the mechanical behaviour of peripheral nerves is dependent of the direction and magnitude of the forces applied to them. This has a direct relation with, for instance, the sequence of movements used to tension the neural structures, either for assessment or intervention purposes. When nerves are tensioned they converge towards the moving joint. Therefore, and as discussed in the study 2, perhaps a long-sitting position should be considered as the starting position for the slump test, when the objective is to add tension to the sciatic nerve. In another example, if the goal is to tension the tibial nerve, maybe ankle dorsiflexion should be applied prior to knee extension during the slump test, or prior to hip flexion during the SLR test.

A question that is frequently debated in the literature is to what extent the information collected during neurodynamics testing is exclusively obtained from the neural tissues. Neurodynamics tests use multi-joint movements to challenge the physical capacity of the peripheral nerves (Coppieters, Stappaerts, Everaert, & Staes, 2001). Consequently, a positive test merely indicates that the neural tissue is mechanosensitive to the applied load (Butler, 2000), meaning that the condition of the tissues surrounding the nerve should not be neglected. The origin of the neural mechanosensitivity may be the product of muscle-tendon or fascia problems. Interestingly, in the study 3, we observed that the neural tension intervention resulted in a decrease of the sciatic stiffness, but without changing the ankle passive torque, and in the absence of significant EMG activity of the semitendinosus muscle. Although nerves are not isolated structures from their mechanical interface, this finding means that neurodynamics interventions based in a slump position can effectively address the sciatic nerve in people with LBRLP, despite its intrinsic relation with the surrounding tissues.

3.2. Clinical potential of SWE

Until few years ago, little was known about the effects of tensile loads applied *in vivo* to human nerves. In an editorial, Shacklock (2005) questions the use of expressions as “adverse neural tension” given that, at that time, there was no way to directly measure the effects of tensile loads applied to the peripheral nerves. Nowadays that situation has changed, and SWE is proven to be a valid method to assess the stiffness of peripheral nerves, with good reproducibility even in dynamic actions, as used in the studies of this thesis. Moreover, SWE has the potential of being used as a complement to neurodynamics testing. Considering the limitations in neurodynamics testing to locate with precision the affected regions, SWE could be used to map the area of a peripheral nerve enabling the detection of regional differences in neural stiffness.

Another possible application of SWE, with high clinical relevance, may be to establish nerve stiffness cutoff values for pathological conditions, similarly to what was accomplished for the median nerve in people with carpal tunnel syndrome (Kantarci et al., 2014), or for the tibial nerve, in people with diabetic neuropathy (Dikici et al., 2016). This would allow for a more precise diagnosis based on the SWV values of the sciatic nerve. In this thesis, despite using a small sample, we observed significant between-limbs differences in the sciatic stiffness, in people with LBRLP. Although it was beyond the scope of this thesis to establish cutoff points for this population, we acknowledge that this would be highly relevant for clinicians, as it would improve diagnostic capabilities, as well as being a valuable tool for revaluation purposes.

CHAPTER VII - Conclusions

The studies compiled in this thesis provide information regarding the clinical and mechanical effects of neurodynamics techniques, which are an intervention commonly used by health professionals to assess and treat people with lower body quadrant dysfunctions. The results observed in this thesis show that not only neurodynamics interventions produce clinical benefits, but can also reduce the stiffness of the sciatic nerve in people with LBRLP, despite the lack of effects found in healthy participants. Future research should continue to explore the effects of neurodynamics techniques, using SWE, a non-invasive method with good reproducibility in measuring the mechanical properties of peripheral nerves.

CHAPTER VIII - References

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